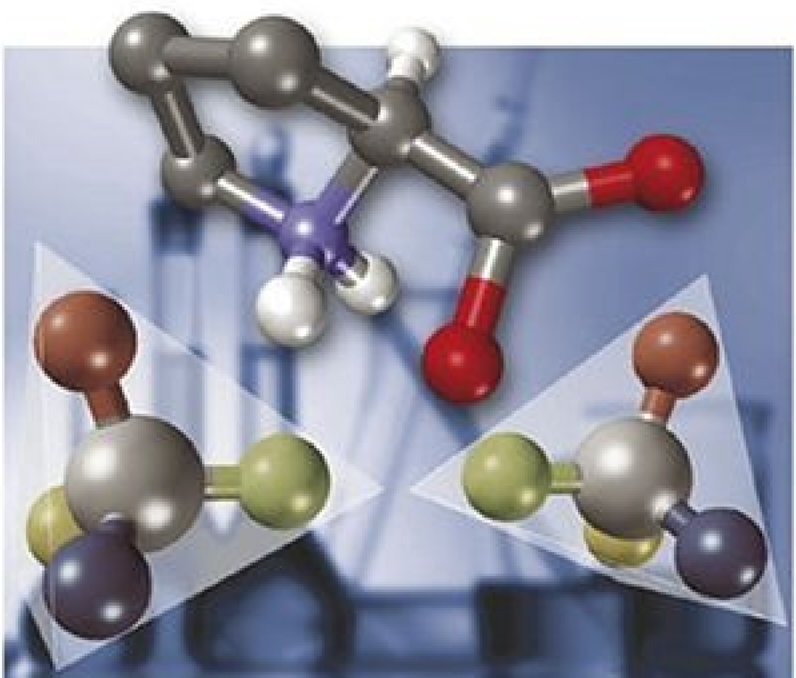
A. Berkessel, H. Gröger

WILEY-VCH

Asymmetric Organocatalysis

From Biomimetic Concepts to Applications in Asymmetric Synthesis



Albrecht Berkessel,
Harald Gröger

Asymmetric Organocatalysis – From Biomimetic Concepts to Applications in Asymmetric Synthesis

Asymmetric Organocatalysis. Albrecht Berkessel and Harald Gröger
Copyright © 2005 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim
ISBN: 3-527-30517-3

Further Reading from Wiley-VCH

A. de Meijere, F. Diederich (Eds.)

Metal-Catalyzed Cross-Coupling Reactions, 2^{nd} Ed., 2 Vols.

2004. 3-527-30518-1

R. Mahrwald (Ed.)

Modern Aldol Reactions, 2 Vols.

2004. 3-527-30714-1

M. Beller, C. Bolm (Eds.)

Transition Metals for Organic Synthesis, 2 Vols., 2^{nd} Ed.

Building Blocks and Fine Chemicals
2004. 3-527-30613-7

N. Krause, A. S. K. Hashmi (Eds.)

Modern Allene Chemistry, 2 Vols.

2004. 3-527-30671-4

J. Zhu, H. Bienaymé (Eds.)

Multicomponent Reactions

2005. 3-527-30806-7

Albrecht Berkessel, Harald Gröger

Asymmetric Organocatalysis – From Biomimetic Concepts to Applications in Asymmetric Synthesis

WILEY-VCH

WILEY-VCH Verlag GmbH & Co. KGaA

Prof. Dr. Albrecht Berkessel
Institut für Organische Chemie
Universität zu Köln
Greinstraße 4
50939 Köln
Germany

Dr. Harald Gröger
Service Center Biocatalysis
Degussa AG
Rodenbacher Chaussee 4
63457 Hanau-Wolfgang
Germany

All books published by Wiley-VCH are carefully produced. Nevertheless, authors and publisher do not warrant the information contained in these books, including this book, to be free of errors. Readers are advised to keep in mind that statements, data, illustrations, procedural details or other items may inadvertently be inaccurate.

Library of Congress Card No.: applied for
A catalogue record for this book is available from the British Library.
Bibliographic information published by Die Deutsche Bibliothek
Die Deutsche Bibliothek lists this publication in the Deutsche Nationalbibliografie; detailed bibliographic data is available in the Internet at http://dnb.ddb.de

© 2005 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim
All rights reserved (including those of translation in other languages). No part of this book may be reproduced in any form – by photoprinting, microfilm, or any other means – nor transmitted or translated into machine language without written permission from the publishers. Registered names, trademarks, etc. used in this book, even when not specifically marked as such, are not to be considered unprotected by law.

Printed in the Federal Republic of Germany.
Printed on acid-free paper.

Typesetting Asco Typesetters, Hong Kong
Printing Strauss GmbH, Mörlenbach
Bookbinding J. Schäffer GmbH, Grünstadt

ISBN-13 978-3-527-30517-9
ISBN-10 3-527-30517-3

Contents

Preface *xi*

Foreword *xiii*

1 **Introduction: Organocatalysis – From Biomimetic Concepts to Powerful Methods for Asymmetric Synthesis** *1*
References *8*

2 **On the Structure of the Book, and a Few General Mechanistic Considerations** *9*
2.1 The Structure of the Book *9*
2.2 General Mechanistic Considerations *9*
References *12*

3 **Nucleophilic Substitution at Aliphatic Carbon** *13*
3.1 α-Alkylation of Cyclic Ketones and Related Compounds *13*
3.2 α-Alkylation of α-Amino Acid Derivatives *16*
3.2.1 Development of Highly Efficient Organocatalysts *16*
3.2.2 Improving Enantioselectivity During Work-up *25*
3.2.3 Specific Application in the Synthesis of Non-natural Amino Acids *25*
3.2.4 Synthesis of α,α-Dialkylated Amino Acids *28*
3.2.5 Enantio- and Diastereoselective Processes – Synthesis of α-Amino Acid Derivatives with Two Stereogenic Centers *30*
3.2.6 Solid-phase Syntheses *31*
3.3 α-Alkylation of Other Acyclic Substrates *33*
3.4 Fluorination, Chlorination, and Bromination Reactions *34*
3.4.1 Fluorination Reactions *34*
3.4.2 Chlorination and Bromination Reactions *38*
References *41*

4 **Nucleophilic Addition to Electron-deficient C=C Double Bonds** *45*
4.1 Intermolecular Michael Addition *45*
4.1.1 Intermolecular Michael Addition of C-nucleophiles *47*
4.1.1.1 Chiral Bases and Phase-transfer Catalysis *47*

Asymmetric Organocatalysis. Albrecht Berkessel and Harald Gröger
Copyright © 2005 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim
ISBN: 3-527-30517-3

4.1.1.2 Activation of Michael Acceptors by Iminium Ion Formation, Activation of Carbonyl Donors by Enamine Formation *55*
4.1.1.3 Addition of C-nucleophiles to Azodicarboxylates *69*
4.1.1.4 Cyclopropanation of Enoates with Phenacyl Halides *70*
4.1.2 Intermolecular Michael Addition of N- and O-nucleophiles *71*
4.1.3 Intermolecular Michael Addition of S- and Se-nucleophiles *73*
4.2 Intramolecular Michael Addition *78*
4.2.1 Intramolecular Michael Addition of C-nucleophiles *78*
4.2.2 Intramolecular Michael Addition of O-nucleophiles *79*
References *82*

5 Nucleophilic Addition to C=N Double Bonds *85*
5.1 Hydrocyanation of Imines (Strecker Reaction) *85*
5.1.1 Chiral Diketopiperazines as Catalysts *85*
5.1.2 Chiral Guanidines as Catalysts *86*
5.1.3 Chiral Ureas and Thioureas as Catalysts *89*
5.1.4 Chiral *N*-Oxides as "Catalysts" *95*
5.2 The Mannich Reaction *97*
5.2.1 Enantioselective Direct Mannich Reaction: Products with One Stereogenic Center *97*
5.2.2 Enantio- and Diastereoselective Direct Mannich Reaction: Products with Two Stereogenic Centers *100*
5.2.3 Proline-catalyzed Mannich Reaction: Process Development and Optimization *104*
5.2.4 Enantioselective Mannich Reaction using Silyl Ketene Acetals *106*
5.3 *β*-Lactam Synthesis *109*
5.4 Sulfur Ylide-based Aziridination of Imines *119*
5.5 Hydrophosphonylation of Imines *126*
References *126*

6 Nucleophilic Addition to C=O Double Bonds *130*
6.1 Hydrocyanation *130*
6.1.1 The Mechanism of the Reaction *132*
6.2 Aldol Reactions *140*
6.2.1 Intermolecular Aldol Reactions *140*
6.2.1.1 Intermolecular Aldol Reaction With Formation of *One* Stereogenic Center *140*
6.2.1.2 Intermolecular Aldol Reaction with Formation of *Two* Stereogenic Centers *154*
6.2.2 Intramolecular Aldol Reaction *166*
6.2.2.1 Intramolecular Aldol Reaction Starting from Diketones *166*
6.2.2.2 Intramolecular Aldol Reaction Starting from Triketones *168*
6.2.2.3 Intramolecular Aldol Reaction Starting from Dialdehydes *174*
6.2.3 Modified Aldol Reactions – Vinylogous Aldol, Nitroaldol, and Nitrone Aldol Reactions *175*
6.3 *β*-Lactone Synthesis *via* Ketene Addition *179*
6.4 The Morita–Baylis–Hillman Reaction *182*

6.5 Allylation Reactions *189*
6.5.1 Chiral Phosphoramides as Organocatalysts *189*
6.5.2 Chiral Formamides as Organocatalysts *197*
6.5.3 Chiral Pyridine Derivatives as Organocatalysts *199*
6.5.4 Chiral *N*-Oxides as Organocatalysts *199*
6.6 Alkylation of C=O Double Bonds *205*
6.7 The Darzens Reaction *205*
6.8 Sulfur Ylide-based Epoxidation of Aldehydes *211*
6.8.1 Epoxide Formation from Ylides Prepared by Means of Bases *212*
6.8.2 Epoxide Formation from Ylides Prepared by Metal-catalyzed Carbene Formation *219*
6.9 The Benzoin Condensation and the Stetter Reaction *227*
6.9.1 The Benzoin Condensation *229*
6.9.2 The Stetter Reaction *231*
6.10 Hydrophosphonylation of C=O Double Bonds *234*
References *236*

7 Nucleophilic Addition to Unsaturated Nitrogen *245*
7.1 Nucleophilic Addition to N=N Double Bonds *245*
7.2 Nucleophilic Addition to N=O Double Bonds *249*
References *254*

8 Cycloaddition Reactions *256*
8.1 [4 + 2]-Cycloadditions – Diels–Alder Reactions *256*
8.1.1 Diels–Alder Reactions Using Alkaloids as Organocatalysts *256*
8.1.2 Diels–Alder and hetero-Diels–Alder Reactions Using α-Amino Acid Derivatives as Organocatalysts *258*
8.1.3 Diels–Alder and hetero-Diels–Alder Reactions Using C_2-symmetric Organocatalysts *261*
8.2 [3 + 2]-Cycloadditions: Nitrone- and Electron-deficient Olefin-based Reactions *262*
References *267*

9 Protonation of Enolates and Tautomerization of Enols *269*
9.1 Enantioselective Protonation of Enolates formed *in situ* from Enolate Precursors *270*
9.2 Enantioselective Tautomerization of Enols Generated *in situ* *271*
9.3 Enantioselective Protonation of Enolates Generated *in situ* from Conjugated Unsaturated Carboxylates *274*
References *275*

10 Oxidation *277*
10.1 Epoxidation of Olefins *277*
10.1.1 Chiral Dioxiranes *277*
10.1.2 Chiral Iminium Ions *287*
10.2 Epoxidation of Enones and Enoates *290*

10.2.1 Chiral Dioxiranes *290*
10.2.2 Peptide Catalysts *290*
10.2.3 Phase-transfer Catalysis *299*
10.3 Sulfoxidation of Thioethers *303*
10.4 Oxidation of Alcohols *306*
10.4.1 Kinetic Resolution of Racemic Alcohols *306*
10.4.2 Desymmetrization of *meso* Diols *308*
References *309*

11 Reduction of Carbonyl Compounds *314*
11.1 Borane Reduction Catalyzed by Oxazaborolidines and Phosphorus-based Catalysts *314*
11.2 Borohydride and Hydrosilane Reduction in the Presence of Phase-transfer Catalysts *318*
11.3 Reduction with Hydrosilanes in the Presence of Chiral Nucleophilic Activators *319*
References *321*

12 Kinetic Resolution of Racemic Alcohols and Amines *323*
12.1 Acylation Reactions *323*
12.2 Redox Reactions *342*
References *345*

13 Desymmetrization and Kinetic Resolution of Anhydrides; Desymmetrization of *meso*-Epoxides and other Prochiral Substrates *347*
13.1 Desymmetrization and Kinetic Resolution of Cyclic Anhydrides *347*
13.1.1 Desymmetrization of Prochiral Cyclic Anhydrides *349*
13.1.2 Kinetic Resolution of Chiral, Racemic Anhydrides *352*
13.1.2.1 Kinetic Resolution of 1,3-Dioxolane-2,4-diones (α-Hydroxy Acid *O*-Carboxy Anhydrides) *352*
13.1.2.2 Kinetic Resolution of *N*-Urethane-protected Amino Acid *N*-Carboxy Anhydrides *355*
13.1.3 Parallel Kinetic Resolution of Chiral, Racemic Anhydrides *358*
13.1.4 Dynamic Kinetic Resolution of Racemic Anhydrides *358*
13.1.4.1 Dynamic Kinetic Resolution of 1,3-Dioxolane-2,4-diones (α-Hydroxy acid *O*-Carboxy Anhydrides) *359*
13.1.4.2 Dynamic Kinetic Resolution of *N*-protected Amino Acid *N*-Carboxy Anhydrides *360*
13.2 Additions to Prochiral Ketenes *363*
13.3 Desymmetrization of *meso*-Diols *366*
13.3.1 Desymmetrization of *meso*-Diols by Acylation *367*
13.3.2 Desymmetrization of *meso*-Diols by Oxidation *371*
13.4 Desymmetrization of *meso*-Epoxides *374*
13.4.1 Enantioselective Isomerization of *meso*-Epoxides to Allylic Alcohols *374*
13.4.2 Enantioselective Ring Opening of *meso*-Epoxides *381*

13.5 The Horner–Wadsworth–Emmons Reaction *383*
13.6 Rearrangement of *O*-Acyl Azlactones, *O*-Acyl Oxindoles, and *O*-Acyl Benzofuranones *385*
References *389*

14 Large-scale Applications of Organocatalysis *393*
14.1 Introduction *393*
14.2 Organocatalysis for Large-scale Applications: Some General Aspects and Considerations *393*
14.2.1 Economy of the Catalyst (Price/Availability) *394*
14.2.2 Stability of the Catalysts and Handling Issues *395*
14.2.3 Recycling Issues: Immobilization of Organocatalysts *395*
14.2.4 Enantioselectivity, Conversion, and Catalytic Loading *396*
14.3 Large-scale Organocatalytic Reaction Processes (Selected Case Studies) *398*
14.3.1 Case Study 1: Julia–Colonna-type Epoxidation *398*
14.3.2 Case Study 2: Hydrocyanation of Imines *401*
14.3.3 Case Study 3: Alkylation of Cyclic Ketones and Glycinates *402*
14.3.4 Case Study 4: The Hajos–Parrish–Eder–Wiechert–Sauer Reaction *405*
References *406*

Appendix: Tabular Survey of Selected Organocatalysts: Reaction Scope and Availability *409*
I Primary and Secondary Amine Catalysts *410*
II Tertiary Amine and Pyridine Catalysts *413*
III Phosphanes *417*
IV Phosphoramidites, Phosphoramides and Formamides *418*
V Ureas, Thioureas, Guanidines, Amidines *420*
VI Ketones *422*
VII Imines, Iminium Cations and Oxazolines *423*
VIII Diols *424*
IX Sulfides *425*
X *N*-Oxides and Nitroxyl Radicals *427*
XI Heterocyclic Carbenes (Carbene Precursors) *429*
XII Peptides *430*
XIII Phase Transfer Catalysts *433*

Index *436*

Preface

What is the incentive for writing a book on "Asymmetric Organocatalysis"? Why should chemists involved in organic synthesis know about the current state and future perspectives of "Asymmetric Organocatalysis"? First of all, efficient catalytic processes lie at the heart of the atom-economic production of enantiomerically pure substances, and the latter are of ever increasing importance as pharmaceuticals, agrochemicals, synthetic intermediates, etc. Until recently, the catalysts employed for the enantioselective synthesis of organic compounds fell almost exclusively into two general categories: transition metal complexes and enzymes. Between the extremes of transition metal catalysis and enzymatic transformations, a third general approach to the catalytic production of enantiomerically pure organic compounds has now emerged: *Asymmetric Organocatalysis*, which is the theme of this book. *Organocatalysts* are purely "organic" molecules, i.e. composed of (mainly) carbon, hydrogen, nitrogen, oxygen, sulfur and phosphorus.

In fact, the historic roots of organocatalysis date back to the first half of the 20th century and the attempt to use low-molecular weight organic compounds to both understand and mimic the catalytic activity and selectivity of enzymes. Before the turn of the century, only a limited number of preparatively useful applications of organocatalysts were reported, such as the proline-catalyzed synthesis of the Wieland-Miescher ketone (the Hajos-Parrish-Eder-Sauer-Wiechert process in the 1970s), and applications of chiral phase-transfer-catalysts in e.g. asymmetric alkylations. The second half of the 20th century saw tremendous progress in the development of transition metal-based catalysis – ultimately culminating in the award of Nobel Prizes to Sharpless, Noyori and Knowles in 2001 – but comparatively little attention was paid to the further development of the promising early applications of purely organic catalysts for asymmetric transformations.

Now, triggered by the ground-breaking work of e.g. *Denmark, Jacobsen, List, MacMillan* and many other researchers in the 1990s and early 2000s, the last decade has seen exponential growth of the field of asymmetric organocatalysis: iminium-, enamine- and phosphoramide-based organocatalysis now allows cycloadditions, *Michael* additions, aldol reactions, nucleophilic substitutions (and many other transformations) with excellent enantioselectivities; new generations of phase-transfer catalysts give almost perfect enantiomeric excesses at low catalyst loadings; chiral ureas and thioureas are extremely enantioselective catalysts for the addition of

various nucleophiles to aldehydes and imines, and so forth. Organocatalysis, by now, has definitely matured to a recognized third methodology, of potential equal status to organometallic and enzymatic catalysis.

Again: Why take the effort to write a book on ''Asymmetric Organocatalysis''? Both authors are deeply committed to the development of novel catalytic methodology, within the academic and the industrial environment, respectively. They both consider asymmetric organocatalysis as a methodology that should be taught to students in up-to-date academic curricula, and should be present in the methodological toolbox of ''established'' chemists dealing with organic synthesis, both in fundamental research and in industrial applications.

This book is in part meant as an introduction to organocatalysis, revealing its historical background, and mostly as a state-of-the-art summary of the methodology available up to early/middle 2004. Organocatalysis has entered the state of a ''gold rush'', and at short intervals, new ''gold mines'' are being discovered and reported in the literature. The reader may forgive the authors if one of his/her favorite catalysts has not made it to the press in time.

Both authors wish to thank Dr. Elke Maase of Wiley-VCH, Weinheim for excellent and most enjoyable collaboration in the course of the preparation of this book!

Cologne and Hanau, December 2004

Albrecht Berkessel
Harald Gröger

Foreword

"Organocatalysis: the word." In the spring of 1998 I became very interested in the notion that small organic molecules could function as efficient and selective catalysts for a large variety of enantioselective transformations. Inspired directly by the work of Shi, Denmark, Yang, Fu, Jacobsen, and Corey, I became convinced of the general need for catalysis strategies or concepts that revolved around small organic catalysts. In that same year we developed an enantioselective organocatalytic Diels Alder reaction based on iminium-activation, to the best of our knowledge a new catalysis concept we hoped would be amenable to many transformations. During the preparation of our Diels Alder manuscript I became interested in coining a new name for what was commonly referred to as "metal-free catalysis". My motivations for doing so were very simple I did not like the idea of describing an area of catalysis in terms of what it was not, and I wanted to invent a specific term that would set this field apart from other types of catalysis. The term "organocatalysis" was born and a field that had existed for at least 40 years acquired a new name. More importantly, with the pioneering work of researchers such as Barbas, List, Jacobsen, and Jørgensen, this field began to receive the attention it had always deserved and the "organocatalysis gold rush" was on.

"Organocatalysis: the field." Over the last ten years the field of organocatalysis has grown from a small collection of chemically unique or unusual reactions to a thriving area of general concepts, atypical reactivity, and widely useful reactions. Although the modern era of organocatalysis remains in its infancy, the pace of growth in this field of chemistry has been nothing short of breathtaking. Indeed, a day hardly passes without a new organocatalytic reaction hitting the electronic chemistry newsstands. It is, therefore, important and timely to have a major text that summarizes the most important developments and concepts in this booming area of catalysis. In this regard, Albrecht Berkessel and Harald Gröger have produced a highly valuable resource for students and researchers in all laboratories working on catalysis and chemical synthesis.

This book is logically presented and lends itself to effortless reading. Because the organization of content has been carefully handled, it is straightforward for the reader to locate and retrieve information. The authors have, moreover, paid considerable attention to providing many of the historical details associated with this

renaissance field. As a result, the readers are provided with a highly accessible text that is as readable as it is educational.

This book will be found both in libraries and on the bookshelves of chemists who enjoy catalysis, chemical synthesis, and the history of our field. Berkessel and Gröger's "Asymmetric Organocatalysis" is the first book to be published in this area and it is likely to be the best monograph in the field for a long time. I hope the authors intend to revise this volume throughout the many exciting times that lie ahead in the field of organocatalysis.

Caltech, September 2004 David MacMillan

1 Introduction: Organocatalysis – From Biomimetic Concepts to Powerful Methods for Asymmetric Synthesis

"Chemists – the transformers of matter". This quotation, taken from the autobiography "The Periodic Table" by Primo Levi, illustrates one of the major goals of chemistry – to provide, in a controlled and economic fashion, valuable products from readily available starting materials. In organic chemistry "value" is directly related to purity; in most instances this implies that an enantiomerically pure product is wanted. In recent years the number of methods available for high-yielding and enantioselective transformation of organic compounds has increased tremendously. Most of the newly introduced reactions are catalytic in nature. Clearly, catalytic transformation provides the best "atom economy", because the stoichiometric introduction and removal of (chiral) auxiliaries can be avoided, or at least minimized [1, 2].

Until recently, the catalysts employed for enantioselective synthesis of organic compounds such as pharmaceutical products, agrochemicals, fine chemicals, or synthetic intermediates, fell into two general categories – transition metal complexes and enzymes. In 2001 the Nobel Prize in Chemistry was awarded to William R. Knowles and Ryoji Noyori "for their work on chirally catalyzed hydrogenation reactions", and to K. Barry Sharpless "for his work on chirally catalyzed oxidation reactions". Could there be a better illustration of the importance of asymmetric catalysis? For all three laureates the development of chiral transition metal catalysts was the key to success. It has been a long-standing belief that only man-made transition metal catalysts can be tailored to produce either of two product enantiomers whereas enzymes cannot. This dogma has been challenged in recent years by tremendous advances in the field of biocatalysis, for example the discovery of preparatively useful enzymes from novel organisms, and the optimization of enzyme performance by selective mutation or by evolutionary methods [3, 4]. The recently issued Wiley–VCH book "Asymmetric Catalysis on Industrial Scale" (edited by H. U. Blaser and E. Schmidt) [5] vividly illustrates the highly competitive head-to-head race between transition metal catalysis and enzymatic catalysis in contemporary industrial production of enantiomerically pure fine chemicals. At the same time, the complementary character of both types of catalyst becomes obvious.

Between the extremes of transition metal catalysis and enzymatic transformations, a third approach to the catalytic production of enantiomerically pure organic compounds has emerged – *organocatalysis*. *Organocatalysts* are purely "organic"

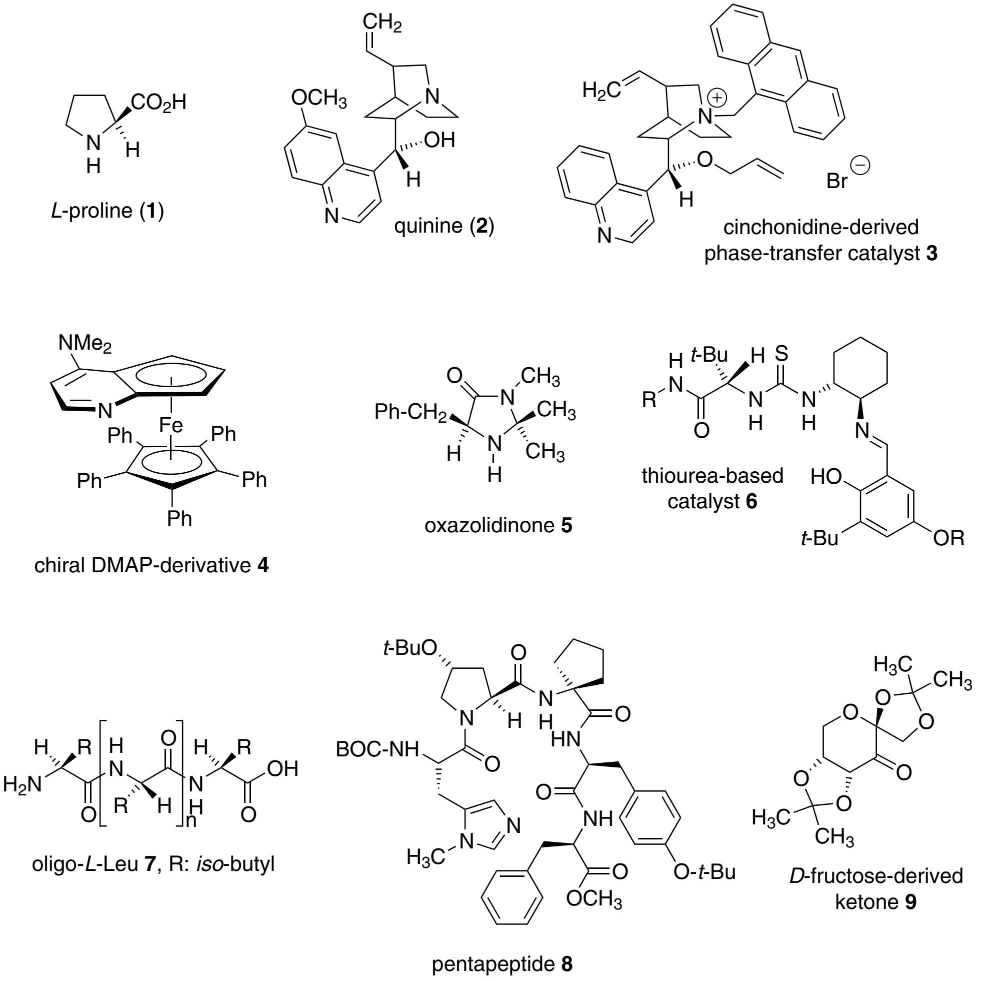
Asymmetric Organocatalysis. Albrecht Berkessel and Harald Gröger
Copyright © 2005 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim
ISBN: 3-527-30517-3

molecules, i.e. composed of (mainly) carbon, hydrogen, nitrogen, sulfur and phosphorus. As opposed to organic ligands in transition metal complexes, the catalytic activity of organocatalysts resides in the low-molecular-weight organic molecule itself, and no transition metals (or other metals) are required. Organocatalysts have several advantages. They are usually robust, inexpensive and readily available, and non-toxic. Because of their inertness toward moisture and oxygen, demanding reaction conditions, for example inert atmosphere, low temperatures, absolute solvents, etc., are, in many instances, not required. Because of the absence of transition metals, organocatalytic methods seem to be especially attractive for the preparation of compounds that do not tolerate metal contamination, e.g. pharmaceutical products. A selection of typical organocatalysts is shown in Scheme 1.1. Proline (**1**), a chiral-pool compound which catalyzes aldol and related reactions by iminium ion or enamine pathways, is a prototypical example (List et al.). The same is true for cinchona alkaloids such as quinine (**2**), which has been abundantly used as a chiral base (Wynberg et al.) or as a chiral nucleophilic catalyst (Bolm et al.) and which has served as the basis for many highly enantioselective phase-transfer catalysts. The latter are exemplified by **3** (Corey, Lygo et al.) which enables, e.g., the alkylation of glycine imines with very high enantioselectivity. The planar chiral DMAP derivative **4** introduced by Fu et al. is extremely selective in several nucleophilic catalyses. Although it is a ferrocene it is regarded an organocatalyst because its "active site" is the pyridine nitrogen atom.

Amino acid-derived organocatalysts such as the oxazolidinone **5** introduced by MacMillan et al. or the chiral thiourea **6** introduced by Jacobsen et al. have enabled excellent enantioselectivity in, e.g., Diels–Alder reactions of α,β-unsaturated aldehydes (oxazolidinone **5**) or the hydrocyanation of imines (thiourea **6**). Peptides, such as oligo-L-leucine (**7**) have found use in the asymmetric epoxidation of enones, the so-called Juliá–Colonna reaction (recently studied by Roberts, Berkessel et al.). Peptides are ideal objects for combinatorial optimization/selection, and the pentapeptide **8** has been identified by Miller et al. as an artificial kinase that enables highly enantioselective phosphorylation. The chiral ketone **9** introduced by Shi et al. is derived from D-fructose and catalyzes the asymmetric epoxidation of a wide range of olefins with persulfate as the oxygen source. This small (and by no means complete) selection of current organocatalysts is intended to illustrate the wide range of reactions that can be catalyzed and the ready accessibility of the organocatalysts applied. With the exception of the planar chiral DMAP derivative **4**, all the organocatalysts shown in Scheme 1.1 are either chiral-pool compounds themselves (**1**, **2**), or they are derived from these readily available sources of chirality by means of a few synthetic steps (**3**, **5**–**9**).

The historic roots of organocatalysis go back to the use of low-molecular-weight compounds in an attempt both to understand and to mimic the catalytic activity and selectivity of enzymes. As early as 1928 the German chemist Wolfgang Langenbeck published on "Analogies in the catalytic action of enzymes and definite organic substances" [6]. The same author coined the term "Organic Catalysts" ("Organische Katalysatoren") [7] and, in 1949, published the second edition (!) of the first book on "Organic Catalysts and their Relation to the Enzymes" ("Die

A selection of typical organocatalysts:

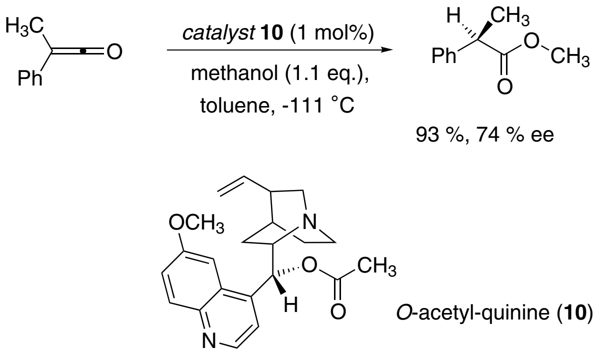


Scheme 1.1

organischen Katalysatoren und ihre Beziehungen zu den Fermenten") [8]. It is fascinating to see that, for example, the use of amino acids as catalysts for aldol reactions was reported for the first time in 1931 [9]. Refs. [6]–[9] also reveal that the conceptual difference between covalent catalysis (called "primary valence catalysis" at that time) and non-covalent catalysis was recognized already and used as a means of categorization of different mechanisms of catalysis. As discussed in Chapter 2, this distinction between "covalent catalysis" and "non-covalent catalysis" is still viable and was clearly a farsighted and revolutionary concept almost 80 years ago.

The first example of an *asymmetric organocatalytic reaction* was reported by Bredig and Fiske as early as 1912, i.e. ca. 90 years ago [10]. These two German chemists reported that addition of HCN to benzaldehyde is accelerated by the alkaloids quinine (**2**) and quinidine and that the resulting cyanohydrins are optically active and of opposite chirality. Unfortunately, the optical yields achieved in most of these early examples were in the range $\leq 10\%$ and thus insufficient for preparative purposes. Pioneering work by Pracejus et al. in 1960, again using alkaloids as catalysts, afforded quite remarkable 74% ee in the addition of methanol to phenylmethylketene. In this particular reaction 1 mol% *O*-acetylquinine (**10**, Scheme 1.2) served as the catalyst [11].

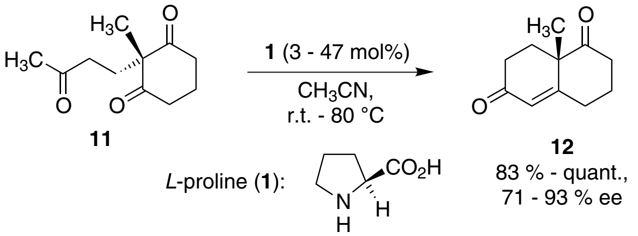
Alkaloid-catalyzed addition of methanol to a prochiral ketene
by *Pracejus et al.* (ref. 11):



Scheme 1.2

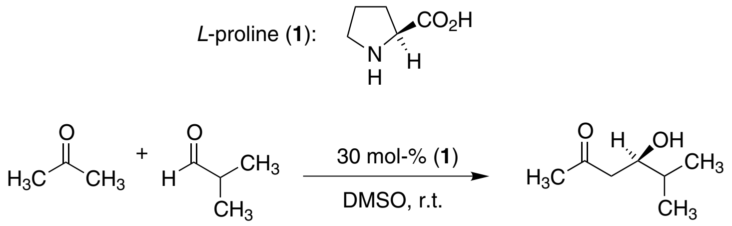
Further breakthroughs in enantioselectivity were achieved in the 1970s and 1980s. For example, 1971 saw the discovery of the Hajos–Parrish–Eder–Sauer–Wiechert reaction, i.e. the proline (**1**)-catalyzed intramolecular asymmetric aldol cyclodehydration of the achiral trione **11** to the unsaturated Wieland–Miescher ketone **12** (Scheme 1.3) [12, 13]. Ketone **12** is an important intermediate in steroid synthesis.

The *Hajos-Parrish-Eder-Sauer-Wiechert*-reaction (refs. 12,13):



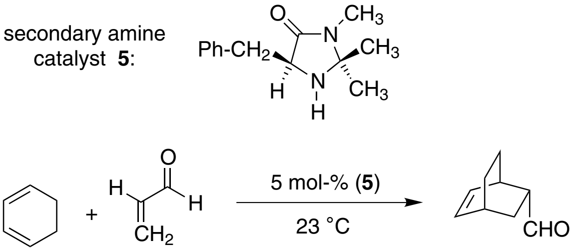
Scheme 1.3

Proline (**1**)-catalyzed intermolecular aldol reaction, *List et al.* (refs. 14,15):



13, 97 %, 96 % ee

Secondary amine **5**-catalyzed Diels-Alder reaction, *MacMillan et al.* (ref. 15):



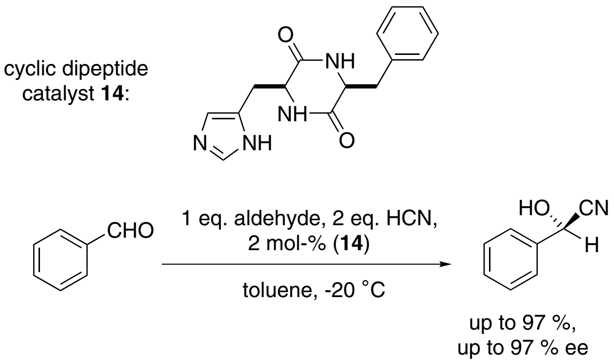
82 %, 94 % ee
(*end/exo* 14:1)

Scheme 1.4

Surprisingly, the catalytic potential of proline (**1**) in asymmetric aldol reactions was not explored further until recently. List et al. reported pioneering studies in 2000 on *inter*molecular aldol reactions [14, 15]. For example, acetone can be added to a variety of aldehydes, affording the corresponding aldols in excellent yields and enantiomeric purity. The example of *iso*-butyraldehyde as acceptor is shown in Scheme 1.4. In this example, the product aldol **13** was obtained in 97% isolated yield and with 96% ee [14, 15]. The remarkable chemo- and enantioselectivity observed by List et al. triggered massive further research activity in proline-catalyzed aldol, Mannich, Michael, and related reactions. In the same year, MacMillan et al. reported that the phenylalanine-derived secondary amine **5** catalyzes the Diels–Alder reaction of α,β-unsaturated aldehydes with enantioselectivity up to 94% (Scheme 1.4) [16]. This initial report by MacMillan et al. was followed by numerous further applications of the catalyst **5** and related secondary amines.

A similarly remarkable event was the discovery of the cyclic peptide **14** shown in Scheme 1.5. In 1981 this cyclic dipeptide – readily available from L-histidine and L-phenylalanine – was reported, by Inoue et al., to catalyze the addition of HCN to

The *cyclo*-*L*-His-*L*-Phe catalyst **14** by *Inoue et al.* (refs. 17,18):

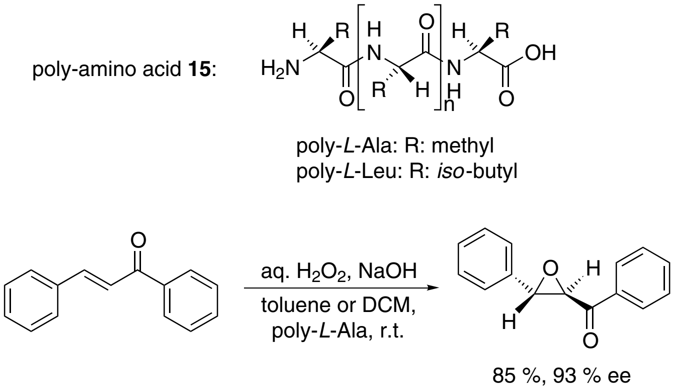


Scheme 1.5

benzaldehyde with up to 90% ee [17, 18] (Scheme 1.5). Again, this observation sparked intensive research in the field of peptide-catalyzed addition of nucleophiles to aldehydes and imines.

Also striking was the discovery, by Juliá, Colonna et al. in the early 1980s, of the poly-amino acid (**15**)-catalyzed epoxidation of chalcones by alkaline hydrogen peroxide [19, 20]. In this experimentally most convenient reaction, enantiomeric excesses > 90% are readily achieved (Scheme 1.6).

The *Juliá-Colonna* epoxidation of chalcones (refs. 19, 20):

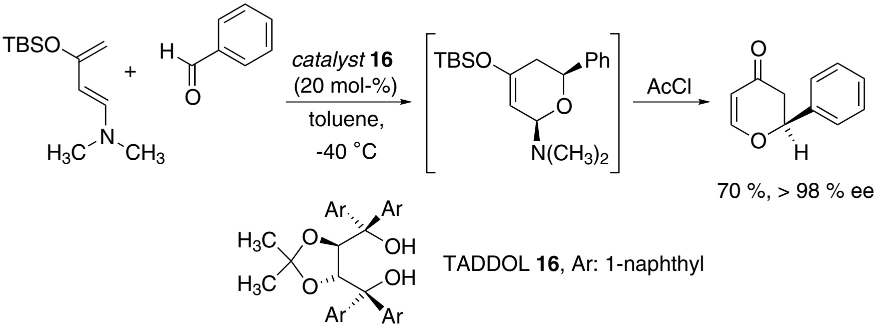


Scheme 1.6

As discussed above, asymmetric organocatalysis is, in principle, an "old" branch of organic chemistry, with its beginnings dating back to the early 20th century (for example the first asymmetric hydrocyanation of an aldehyde in 1912). This

initial phase of organocatalysis was, however, mainly mechanistic/biomimetic in nature, and the relatively low enantiomeric excess achieved prohibited "real" synthetic applications. Isolated examples of highly enantioselective organocatalytic processes were reported in the 1960s to the 1980s, for example the alkaloid-catalyzed addition of alcohols to prochiral ketenes by Pracejus et al. (Scheme 1.2) [11], the Hajos–Parrish–Eder–Sauer–Wiechert reaction (Scheme 1.3) [12, 13], the hydrocyanantion of aldehydes using the Inoue catalyst **14** (Scheme 1.5) [17, 18], or the Juliá–Colonna epoxidation (Scheme 1.6) [19, 20], but the field still remained "sub-critical". Now, triggered by the ground-breaking work of List, MacMillan, and others in the early 2000s, the last ca. five years have seen exponential growth of the field of asymmetric organocatalysis. Iminium and enamine-based organocatalysis now enables cycloadditions, Michael additions, aldol reactions, nucleophilic substitutions, and many other transformations with excellent enantioselectivity; new generations of phase-transfer catalysts give almost perfect enantiomeric excesses at low catalyst loadings; chiral ureas and thioureas are extremely enantioselective catalysts for addition of a variety of nucleophiles to aldehydes and imines; and so forth. Organocatalysis currently seems to be in the state of a "gold rush" and at short intervals new "gold mines" are discovered and reported in the literature. A very recent example is the finding by Rawal et al. that hetero-Diels–Alder reactions – a classical domain of metal-based Lewis acids – can be effected with very high enantioselectivity by hydrogen bonding to chiral diols such as TADDOL (**16**, Scheme 1.7) [21].

The TADDOL (**16**) catalyzed hetero-*Diels-Alder*-reaction
by *Rawal et al.* (ref. 21):



Scheme 1.7

Compared with earlier approaches, both prospecting and exploiting of the fields is greatly aided and accelerated by advanced analytical technology and, in particular, by synergism with theoretical and computational chemistry. Overall, asymmetric organocatalysis has matured in recent few years into a very powerful, practical, and broadly applicable third methodological approach in catalytic asymmetric

synthesis [22]. This book is meant as a "mise au point" dated 2005; it is hoped it will satisfy the expectations of readers looking for up-to-date information on the best organocatalytic methods currently available for a given synthetic problem and those of readers interested in the development of the field.

References

1. B. M. Trost, *Science* **1991**, *254*, 1471–1477.
2. B. M. Trost, *Angew. Chem.* **1995**, *107*, 285–307; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 259–281.
3. (a) M. T. Reetz, *Enzyme Functionality* **2004**, 559–598; (b) K. Drauz, H. Waldmann (eds), *Enzyme Catalysis in Organic Synthesis*, Wiley–VCH, Weinheim, 2002.
4. (a) T. Eggert, K.-E. Jaeger, M. T. Reetz, *Enzyme Functionality* **2004**, 375–390; (b) M. T. Reetz, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5716–5722; (c) M. Bocola, N. Otte, K.-E. Jaeger, M. T. Reetz, W. Thiel, *ChemBioChem* **2004**, *5*, 214–223; (d) M. T. Reetz, *Angew. Chem.* **2001**, *113*, 292–320; *Angew. Chem. Int. Ed.* **2001**, *40*, 284–310; (e) S. Brakmann, K. Johnsson (eds), *Directed Molecular Evolution of Proteins*, Wiley–VCH, Weinheim, 2002.
5. H. U. Blaser, E. Schmidt (eds.), *Asymmetric Catalysis on Industrial Scale*, Wiley-VCH, Weinheim, 2004.
6. W. Langenbeck, *Angew. Chem.* **1928**, *41*, 740–745.
7. W. Langenbeck, *Angew. Chem.* **1932**, *45*, 97–99.
8. W. Langenbeck, *Die organischen Katalysatoren und ihre Beziehungen zu den Fermenten*, 2nd ed., Springer, Berlin, 1949.
9. (a) F. G. Fischer, A. Marschall, *Ber.* **1931**, *64*, 2825–2827; (b) W. Langenbeck, G. Borth, *Ber.* **1942**, *75B*, 951–953.
10. G. Bredig, W. S. Fiske, *Biochem. Z.* **1912**, 7.
11. (a) H. Pracejus, *Justus Liebigs Ann. Chem.* **1960**, *634*, 9–22; (b) H. Pracejus, H. Mätje, *J. Prakt. Chem.* **1964**, *24*, 195–205.
12. U. Eder, G. Sauer, R. Wiechert, *Angew. Chem.* **1971**, *83*, 492–493; *Angew. Chem. Int. Ed.* **1971**, *10*, 496–497.
13. Z. G. Hajos, D. R. Parrish, *J. Org. Chem.* **1974**, *39*, 1615–1621.
14. B. List, R. A. Lerner, C. F. Barbas III, *J. Am. Chem. Soc.* **2000**, *122*, 2395–2396.
15. B. List, *Tetrahedron* **2002**, *58*, 5573–5590.
16. K. A. Ahrendt, C. J. Borths, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2000**, *122*, 4243–4244.
17. J. Oku, S. Inoue, *J. Chem. Soc., Chem. Commun.* **1981**, 229–230.
18. J.-I. Oku, N. Ito, S. Inoue, *Macromol. Chem.* **1982**, *183*, 579–589.
19. S. Juliá, J. Guixer, J. Masana, J. Rocas, S. Colonna, R. Annuziata, H. Molinari, *J. Chem. Soc., Perkin Trans. 1* **1982**, 1317–1324.
20. S. Juliá, J. Masana, J. C. Vega, *Angew. Chem.* **1980**, *92*, 968–969; *Angew. Chem. Int. Ed. Engl.* **1980**, *19*, 929.
21. Y. Huang, A. K. Unni, A. N. Thadani, V. H. Rawal, *Nature* **2003**, *424*, 146.
22. For recent reviews on asymmetric organocatalysis, see: (a) *Acc. Chem. Res.* **2004**, *37*, issue 8; (b) *Adv. Symth. Catal.* **2004**, *346*, issue 9+10; (c) P. I. Daiko, L. Moisan, *Angew. Chem.* **2004**, *116*, 5248–5286; *Angew. Chem. Int. Ed.* **2004**, *43*, 5138–5175.

2
On the Structure of the Book, and a Few General Mechanistic Considerations

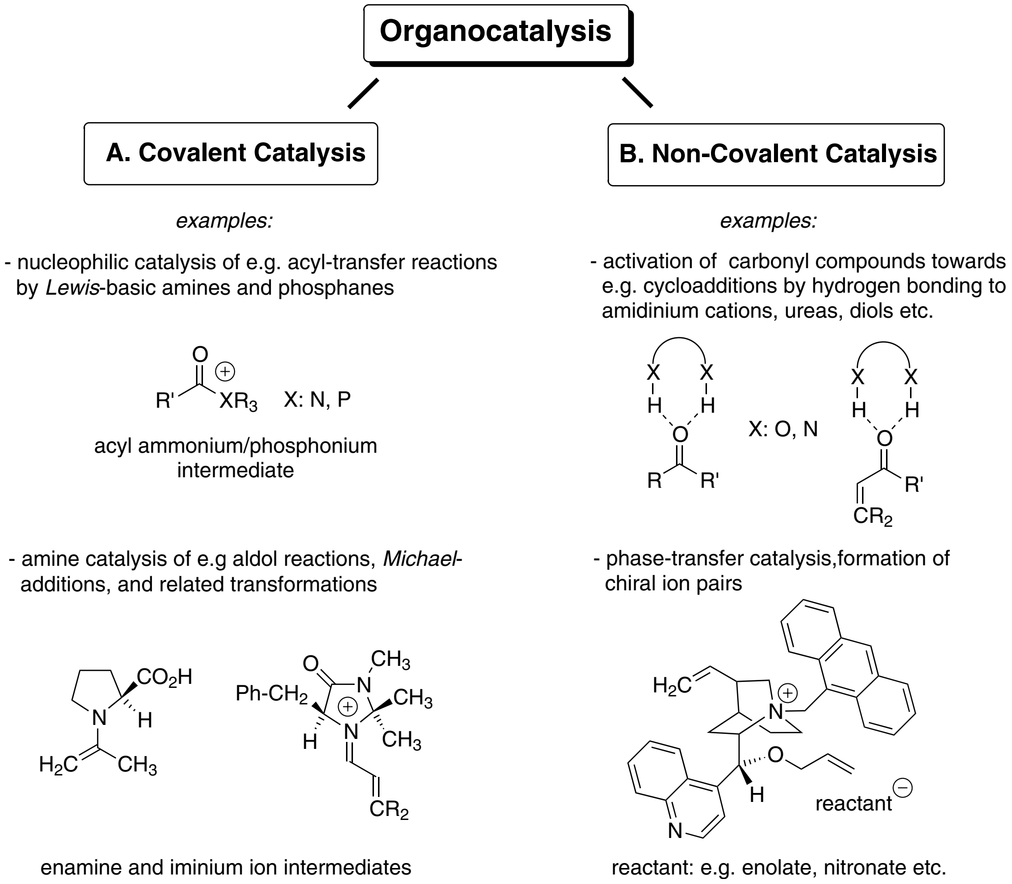
2.1
The Structure of the Book

Two similarly attractive possibilities were considered for ordering the many examples of organocatalytic processes reported in the literature – by the *type of catalyst* employed or by the *type of reaction catalyzed.* As mentioned in the introduction, Chapter 1, the major goal of this book is to provide up-to-date information about the organocatalytic methods currently available for solution of a given synthetic problem. Chapters 3–13 are, therefore, arranged according to the type of organocatalytic reaction, for example aldol reactions, cycloadditions, desymmetrization of meso anhydrides, etc. Each chapter ends with a "Conclusion", a brief summary of the state of the art for the type of reaction under discussion. Most of the work reported and discussed in Chapters 3–13 originated from academic laboratories and these chapters deal mainly with "academic aspects" of synthesis and catalysis. Chapter 14, on the other hand, provides examples of organocatalytic processes applied in an industrial environment. Finally, the appendix lists prominent and frequently applied organocatalysts, together with the reaction types for which they have been used. Availability is commented on, and references to the corresponding chapters of this book are provided.

2.2
General Mechanistic Considerations

As discussed above, this book is ordered according to the different types of reaction being catalyzed. It should be noted, however, that there are only a rather limited number of "mechanistic categories" to which all these reactions can be assigned. The mechanisms by which metal-free enzymes (the majority of enzymes do not contain catalytically active metals) effect dramatic rate accelerations have been a major field of research in bioorganic chemistry for decades [1–6]. In many instances organocatalysts can be regarded as "minimum versions" of metal-free enzymes, and the mechanisms and categories of enzymatic catalysis apply to the action of organocatalysts also. In both cases the rate accelerations observed depend on typical interactions between organic molecules. A general distinction can be

Asymmetric Organocatalysis. Albrecht Berkessel and Harald Gröger
Copyright © 2005 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim
ISBN: 3-527-30517-3

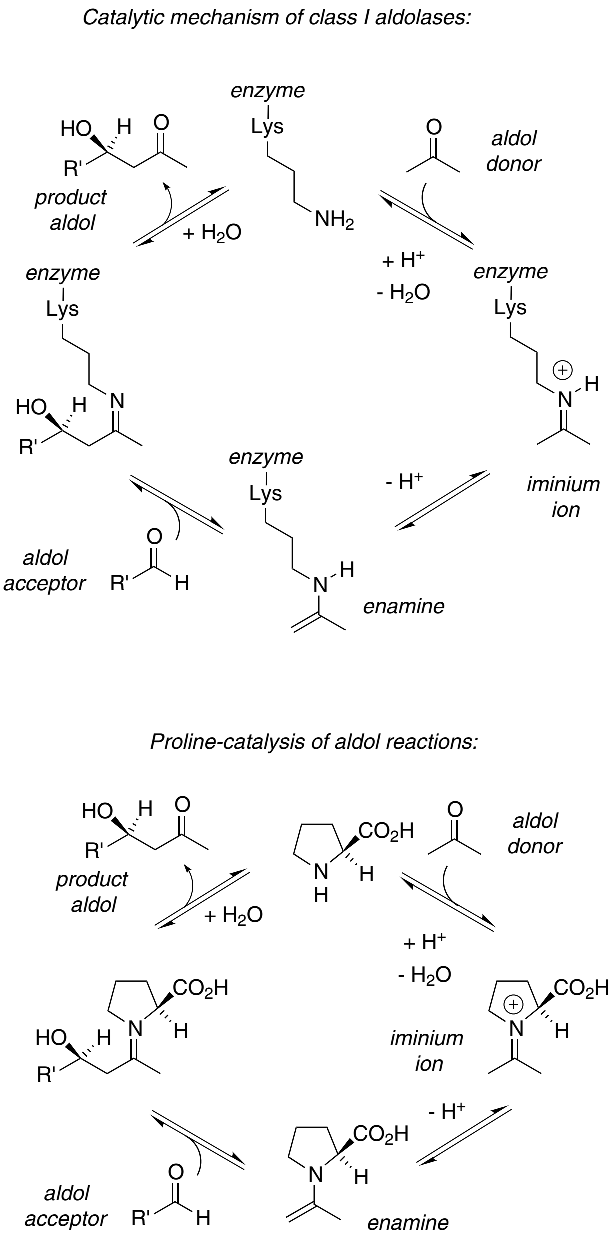


Scheme 2.1

made between processes that involve the *formation of covalent adducts* between catalyst and substrate(s) within the catalytic cycle and processes that rely on *non-covalent interactions* such as hydrogen bonding or the formation of ion pairs. The former interaction has been termed ''covalent catalysis'' and the latter situation is usually denoted ''non-covalent catalysis'' (Scheme 2.1).

The formation of covalent substrate–catalyst adducts might occur, e.g., by single-step Lewis-acid–Lewis-base interaction or by multi-step reactions such as the formation of enamines from aldehydes and secondary amines. The catalysis of aldol reactions by formation of the donor enamine is a striking example of common mechanisms in enzymatic catalysis and organocatalysis – in class-I aldolases lysine provides the catalytically active amine group whereas typical organocatalysts for this purpose are secondary amines, the most simple being proline (Scheme 2.2).

In many instances non-covalent catalysis relies on the formation of hydrogen-


Catalytic mechanism of class I aldolases:
enzyme
Lys
NH2
HO
H
O
R'
product aldol
+ H2O
O
aldol donor
+ H+
- H2O
enzyme
Lys
N
iminium ion
- H+
enzyme
Lys
N
H
enamine
aldol acceptor
R'
H
Proline-catalysis of aldol reactions:
CO2H
N
H
product aldol
aldol donor
iminium ion
enamine
aldol acceptor

Scheme 2.2

bonded adducts between substrate and catalyst or on protonation/deprotonation processes. Phase-transfer catalysis (PTC) by organic phase-transfer catalysts also falls into the category "non-covalent catalysis". It is, however, mechanistically unique, because PTC promotes reactivity not only by altering the chemical properties of the reactants but also involves a transport phenomenon. It is tempting to speculate whether "covalent forms" of PTC might also be feasible.

Specific mechanistic information on the organocatalytic processes discussed in this book is given in the individual chapters.

References

1 For a very early account on enzymatic catalysis and organocatalysis, and their analogies, see: W. Langenbeck, *Die organischen Katalysatoren und ihre Beziehungen zu den Fermenten (Organic Catalysts and their Relation to the Enzymes)*, 2nd ed., Springer, Berlin, 1949.

2 M. Page, A. Williams, *Organic and Bio-Organic Mechanisms*, Longman, Harlow, 1997.

3 H. Dugas, *Biorganic Chemistry: A Chemical Approach to Enzyme Action*, 3rd edn, Springer, New York, 1991.

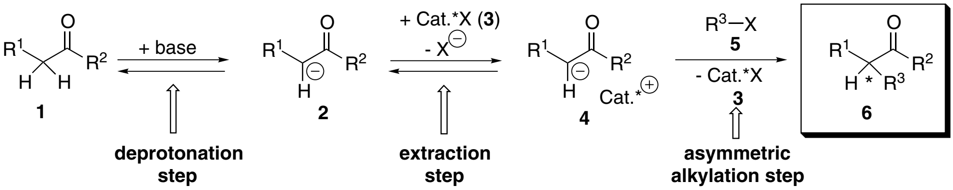
4 A. J. Kirby, *Angew. Chem.* **1996**, *108*, 770–790; *Angew. Chem. Int. Ed.* **1996**, *35*, 707–724.

5 R. Breslow, *Chem. Biol.* **1998**, *5*, R-27–R-28.

6 R. Breslow, *J. Chem. Educ.* **1998**, *75*, 705–718.

3
Nucleophilic Substitution at Aliphatic Carbon

Enantioselective catalytic alkylation is a versatile method for construction of stereogenic carbon centers. Typically, phase-transfer catalysts are used and form a chiral ion pair of type **4** as an key intermediate. In a first step, an anion, **2**, is formed *via* deprotonation with an achiral base; this is followed by extraction in the organic phase via formation of a salt complex of type **4** with the phase-transfer organocatalyst, **3**. Subsequently, a nucleophilic substitution reaction furnishes the optically active alkylated products of type **6**, with recovery of the catalyst **3**. An overview of this reaction concept is given in Scheme 3.1 [1].



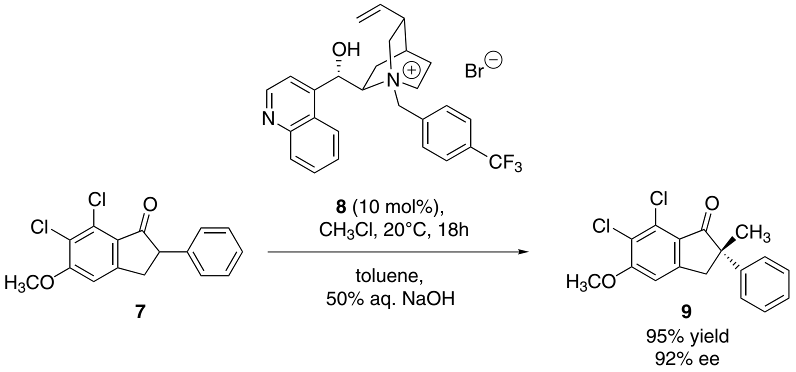
Scheme 3.1

An important issue is the right choice of substrate **1** which functions as an anion precursor. Successful organocatalytic conversions have been reported with indanones and benzophenone imines of glycine derivatives. The latter compounds are, in particular, useful for the synthesis of optically active α-amino acids. Excellent enantioselectivity has been reported for these conversions. In the following text the main achievements in this field of asymmetric organocatalytic nucleophilic substitutions are summarized [1, 2]. The related addition of the anions **2** to Michael-acceptors is covered by chapter 4.

3.1
α-Alkylation of Cyclic Ketones and Related Compounds

The first example of the use of an alkaloid-based chiral phase-transfer catalyst as an efficient organocatalyst for enantioselective alkylation reactions was reported in 1984 [3, 4]. Researchers from Merck used a cinchoninium bromide, **8**, as a catalyst

Asymmetric Organocatalysis. Albrecht Berkessel and Harald Gröger
Copyright © 2005 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim
ISBN: 3-527-30517-3



Scheme 3.2

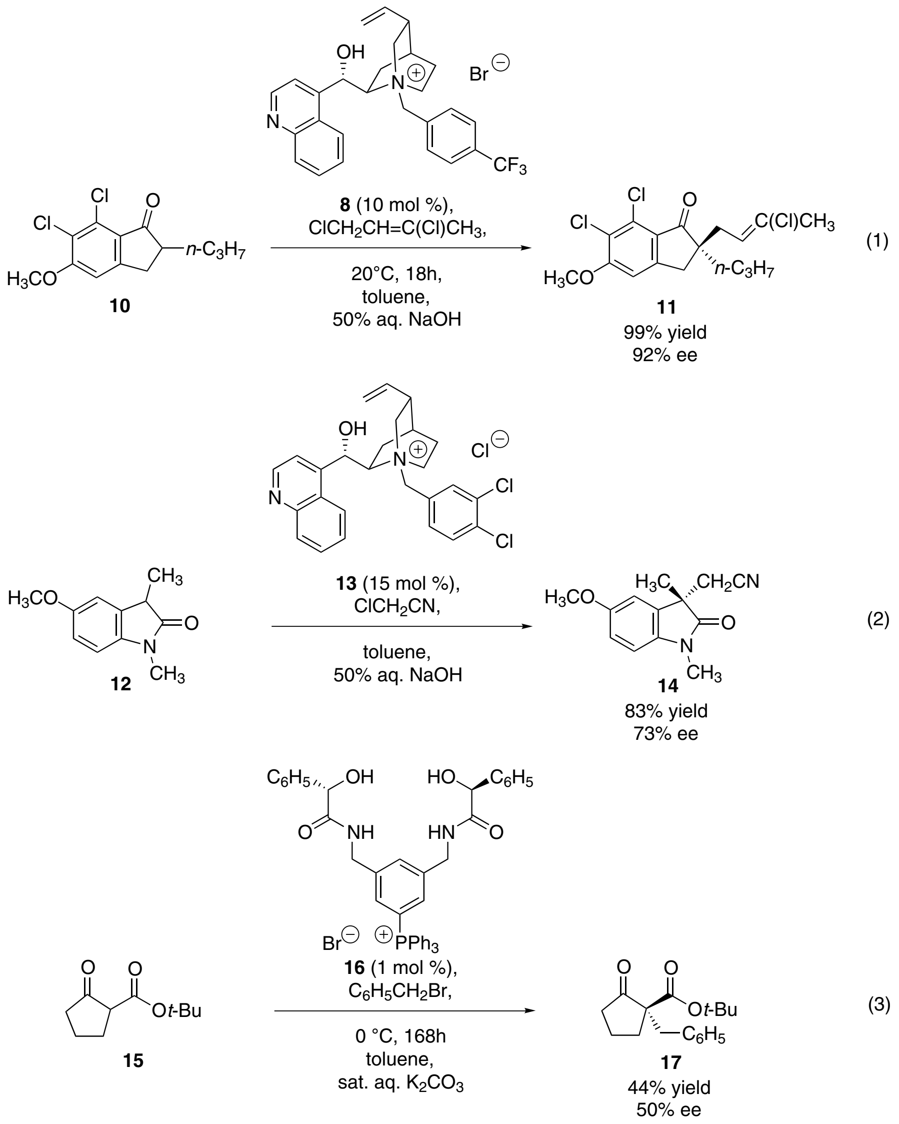
in the methylation of the 2-substituted indanone **7**. The desired product, **9**, a key intermediate in the synthesis of (+)-indacrinone was formed in 95% yield and with 92% ee (Scheme 3.2) [3]. After detailed study of the effects of solvent, alkylating agent, temperature, and catalysts, improvement of enantioselectivity up to 94% ee was achieved [5].

The catalyst concentration, which was varied between 10 and 50 mol%, controlled the rate of the reaction but did not have a significant effect on enantioselectivity [3]. Use of methyl chloride as methylating agent resulted in higher enantioselectivity than methyl bromide or iodide. In general, non-polar solvents, e.g. toluene, resulted in higher enantioselectivity than polar solvents. In addition, higher ee values were obtained after greater dilution of the reaction mixture [3]. Kinetic and mechanistic studies [5] revealed several unusual features. For example, depending on the concentration of sodium hydroxide (50% or 30%) a solid sodium enolate can be formed in the initial stage [5]. The high enantioselectivity was rationalized in terms of formation of a tight ion pair between the catalyst and the indanone enolate.

The broad substrate range, in particular with regard to the alkyl halide component, led to numerous interesting applications of this asymmetric phase-transfer-catalyzed alkylation using alkaloids as catalyst [6–18]. Selected examples are described below.

When the reaction is performed using 1,3-dichloro-2-butene as the alkyl halide, the indanone derivative **11** is formed in excellent yield (99%) and with high (92%) ee (Scheme 3.3, Eq. 1) [6]. Products of type **11** are interesting intermediates for preparation of optically active tricyclic enones, which are obtained after hydrolysis and Robinson annelation [6].

Organocatalytic asymmetric alkylation methodology has also been efficiently applied in a practical multi-gram synthesis of pharmaceutically interesting, optically active (−)-physostigmine analogs [7]. In the presence of 15 mol% of the catalyst **13** alkylation of the oxindole substrate **12** with chloroacetonitrile furnished the desired product **14** in 83% yield and 73% ee (Scheme 3.3, Eq. 2). The counter-ion of the



Scheme 3.3

phase-transfer catalyst, **13**, did not seem to play a major role in this reaction, because similar results were obtained by use of the chloride and bromide salts. The asymmetric alkylation of oxindoles of type **12** has been also extended to other alkyl halides as electrophiles [7].

Derivatives of commercially available alkaloids, e.g. **8** and **13**, have usually been used as the phase-transfer catalyst. Besides these "classic standard" catalysts, however, efforts have been also made to design novel organocatalysts with new proper-

ties. The development of such a new type of organocatalyst suitable for asymmetric alkylation reactions has recently been reported by Manabe (Scheme 3.3, Eq. 3) [14]. In the presence of the chiral phosphonium salt **16** as organocatalyst asymmetric alkylation proceeds with formation of the desired products **17** in satisfactory to good yields (37–80%) and enantioselectivity up to 50%.

3.2
α-Alkylation of α-Amino Acid Derivatives

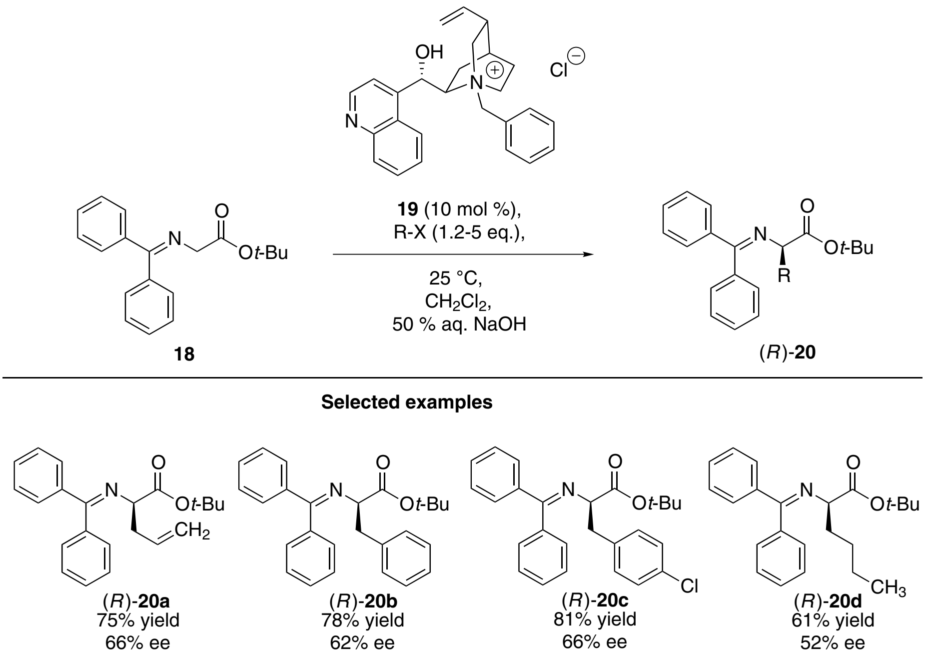
The use of benzophenone imines of glycine derivatives [19] as substrates in enantioselective organocatalytic alkylation has been developed toward an excellent method for preparation of a wide range of optically active α-amino acids with high enantioselectivity [1, 20].

3.2.1
Development of Highly Efficient Organocatalysts

In an early contribution (1989) the O'Donnell group reported the first example of this type of asymmetric alkylation [21]. In the presence of 10 mol% of the cinchonine-derived organocatalyst **19** the desired products of type **20** were obtained in good chemical yields (up to 82%) and enantioselectivity up to 66% ee. Use of the *tert*-butyl ester led to the best results. Investigation of the effect of aqueous sodium hydroxide revealed the beneficial effect of increased concentrations with regard to enantioselectivity and shorter reaction times. This alkaloid-catalyzed alkylation has been successfully performed with a broad variety of alkyl halides as starting material [21]. Selected examples of this asymmetric organocatalytic synthesis of α-amino acid derivatives are shown in Scheme 3.4. It is worthy of note that this reaction was successfully performed on a multi-gram scale. In addition, recrystallization and subsequent hydrolysis gave the "free" amino acid as an enantiomerically pure sample. For example, 6.5 g D-*p*-chlorophenylalanine were prepared by use of this practical procedure developed by O'Donnell and co-workers [21].

The opposite enantiomers can be obtained easily simply by changing from the cinchonine-derived catalyst to the cinchonidine analog [21]. This contribution by O'Donnell et al. served as a starting point for impressive studies from several groups with regard to detailed optimization of the process.

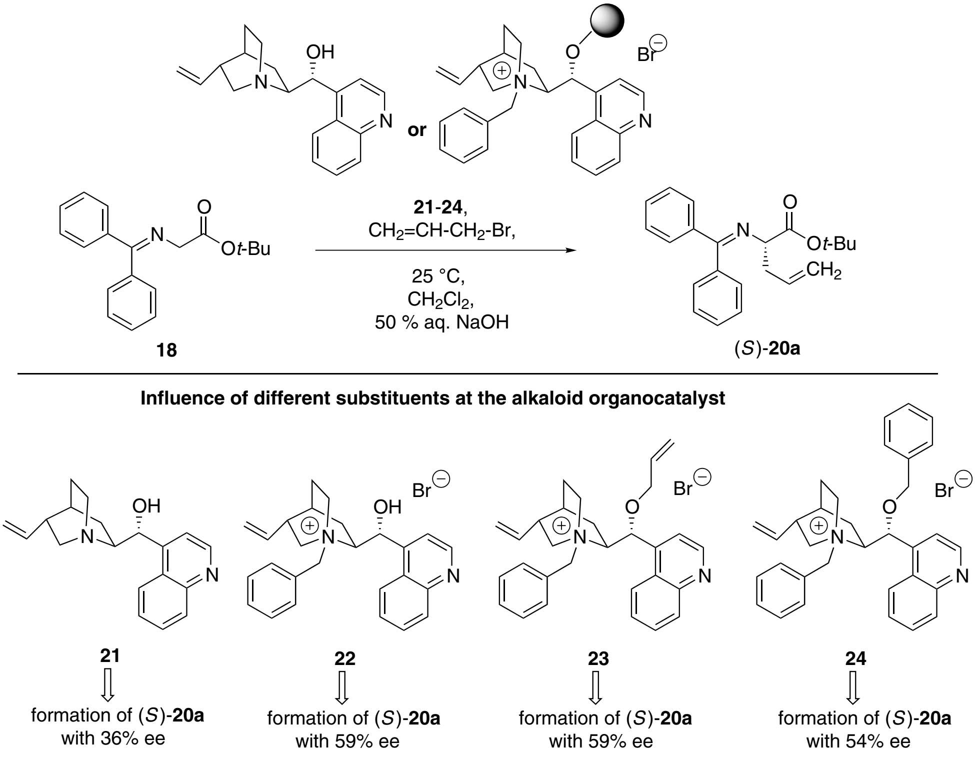
Optimization of the alkaloid phase-transfer catalysts included both the development of improved reaction conditions and the design of more efficient organocatalysts. Addressing this latter issue, O'Donnell observed the first remarkable improvement of the enantioselectivity on use of modified alkaloid organocatalysts with an *O*-substituent, in particular an *O*-allyl or *O*-benzyl substituent, for example **23** and **24**, respectively. This positive effect of *O*-alkylated structures was discovered during a detailed mechanistic study [22]. In this study it was found that *O*-alkylation of the previously used alkaloid catalysts, e.g. **21**, and *N*-alkylated derivatives thereof, e.g. **22**, by reaction with an alkyl halide (which is used in 1.2–5



Scheme 3.4

equiv. excess) proceeds *in situ*, and that the resulting *O*-alkylated alkaloids are, in fact, the catalytically active species. Accordingly, the organocatalysts **22–24** gave comparable results with regard to enantioselectivity. The *N*-benzyl group was also found to be beneficial, because better enantioselectivity was obtained with phase-transfer catalysts **22–24** (which are all *N*-benzylated) compared with somewhat lower ee of 36% with cinchonidine, **21**, which is *N*-allylated during the reaction (Scheme 3.5). In Scheme 3.5 the effect on enantioselectivity of different substituents on the alkaloid organocatalyst is summarized for a model reaction. Applying organocatalysts of type **23–24** in the alkylation reactions led to enantioselectivity of up to 81% ee [20–24].

Finally, further improvement of the enantioselectivity with a "jump" of ee values to the range > 90% ee was achieved independently by the Corey and Lygo groups [25–27]. Based on a rational approach, and previous findings that attachment of the 9-anthracenylmethyl group to a bridgehead nitrogen gave high enantioselectivity in the biscinchona-alkaloid-catalyzed dihydroxylation of olefins by osmium tetroxide [28], Corey and co-workers designed the structurally rigidified chiral quaternary ammonium salt **25** (Scheme 3.6) [25]. Use of 10 mol% of this compound **25** as an organocatalyst in asymmetric alkylation reactions revealed its high catalytic potential with excellent enantioselectivity of up to 99.5% ee [25a]. In general, enantioselectivity was in the range 92 to 99.5% ee; this was accompanied by yields in the range 67 to 91%. Selected preparative examples are shown in Scheme 3.6. As the basic phase, solid cesium hydroxide monohydrate was used instead of 50%

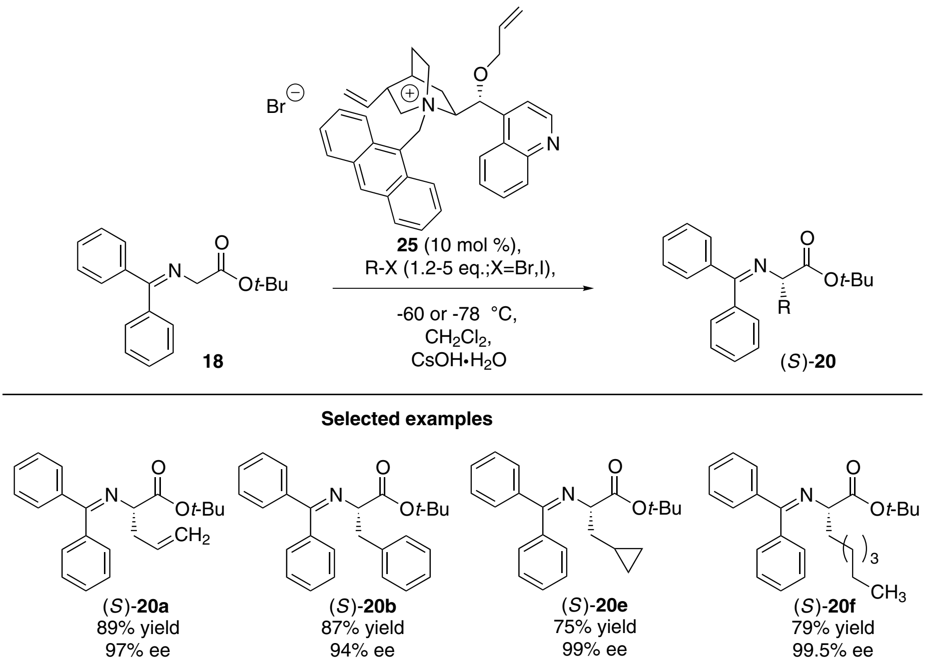


Scheme 3.5

aqueous sodium hydroxide to minimize the water content of the organic phase and to enable work at lower reaction temperatures of −60 to −78 °C.

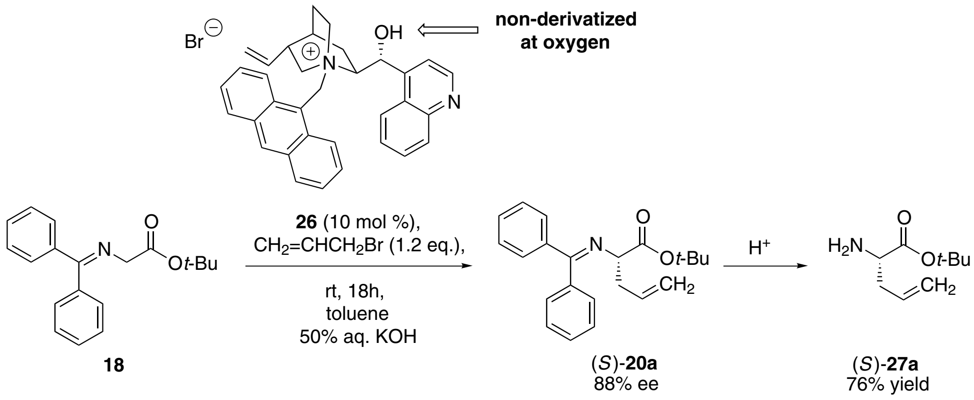
A similar approach was reported by Lygo and co-workers who applied comparable anthracenylmethyl-based ammonium salts of type **26** in combination with 50% aqueous potassium hydroxide as a basic system at room temperature [26, 27a]. Under these conditions the required *O*-alkylation at the alkaloid catalyst's hydroxyl group occurs *in situ*. The enantioselective alkylation reactions proceeded with somewhat lower enantioselectivity (up to 91% ee) compared with the results obtained with the Corey catalyst **25**. The overall yields of esters of type **27** (obtained after imine hydrolysis) were in the range 40 to 86% [26]. A selected example is shown in Scheme 3.7. Because the pseudo-enantiomeric catalyst pairs **25** and **26** led to opposite enantiomers with comparable enantioselectivity, this procedure enables convenient access to both enantiomers. Recently, the Lygo group reported an *in situ*-preparation of the alkaloid-based phase transfer catalyst [27b] as well as the application of a new, highly effective phase-transfer catalyst derived from α-methylnaphthylamine, which was found by screening of a catalyst library [27c].

The development of dimeric cinchona alkaloids as very efficient and practical catalysts for asymmetric alkylation of the *N*-protected glycine ester **18** was reported

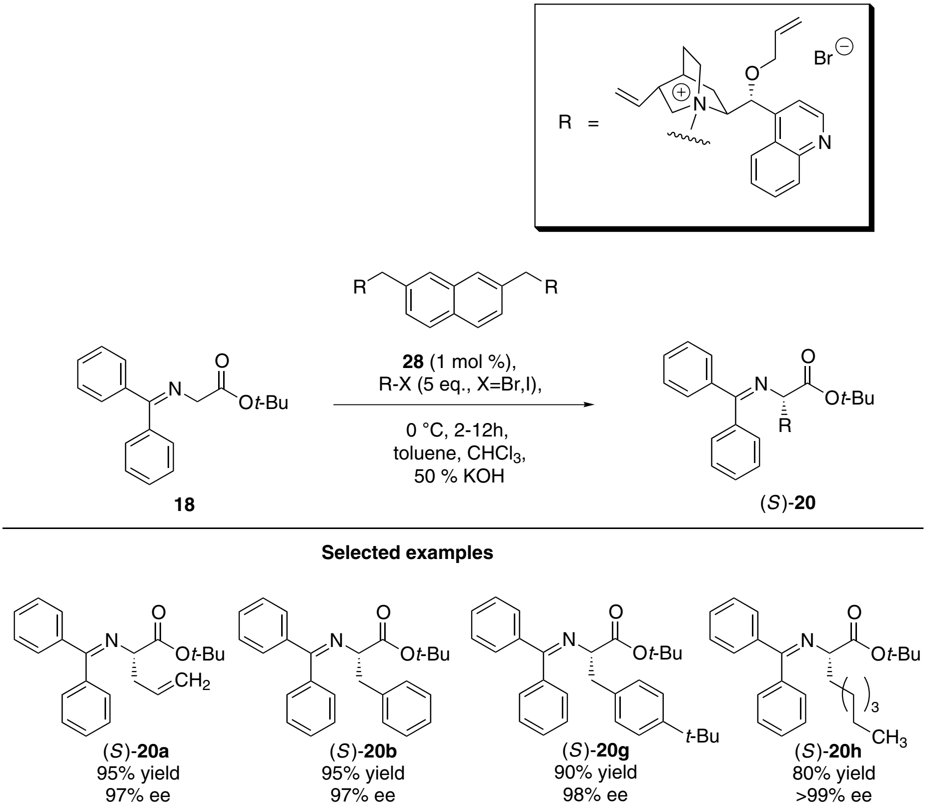


Scheme 3.6

by the Park and Jew group [29–31]. When the naphthalene-based ammonium salt **28** is used the alkylation proceeds with formation of the amino acid derivatives **20** in high yields in the range of 80–95% and excellent enantioselectivity of 96 to >99% ee with a broad variety of alkyl halides [29]. Selected examples are shown in Scheme 3.8. For example, starting from hexyl iodide a yield of 95% and >99% ee were obtained for the product (*S*)-**20h**. It should be noted that investigation of



Scheme 3.7

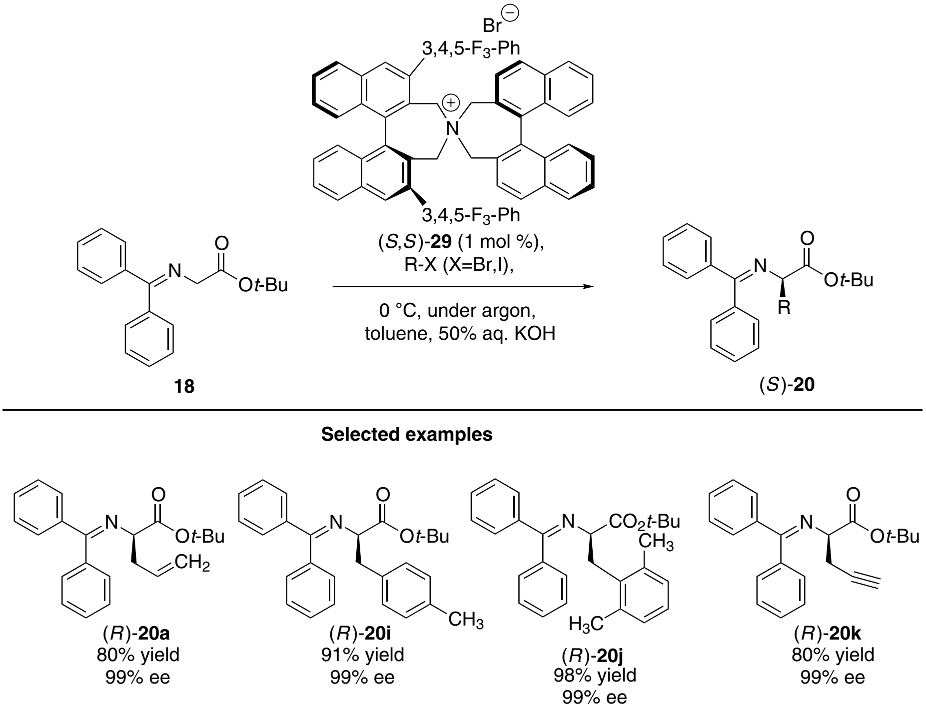


Scheme 3.8

the substrate range was conducted with a catalytic amount of 1 mol% only. The reaction time was 2–12 h. The Park and Jew group also reported the use of other types of related dimeric cinchona alkaloids, prepared from cinchonidine and α,α-dibromoxylene [30], and of trimeric ammonium salts [31]. Use of these chiral phase-transfer alkaloid catalysts also led to high enantioselectivity, emphasizing the high efficiency in asymmetric alkylation reactions of catalysts bearing two cinchona alkaloids units attached to a spacer [30, 31].

Dimeric phase-transfer catalysts were also reported by Najera et al., who used cinchonidine- and cinchonine-derived ammonium salts bearing a dimethylanthracenyl bridge as a spacer [32]. In the presence of these catalysts high enantioselectivity of up to 90% ee was obtained.

A new class of suitable optically active organocatalyst for enantioselective alkylations has recently been developed by Maruoka and co-workers [1e, 33–37]. This catalyst is not based on an alkaloid-related quaternary ammonium salt but consists of a C_2-symmetric compound of type **29** (or derivatives thereof bearing other types of substituent on the 3,3′ positions of the binaphthyl unit) [33, 34]. In the presence

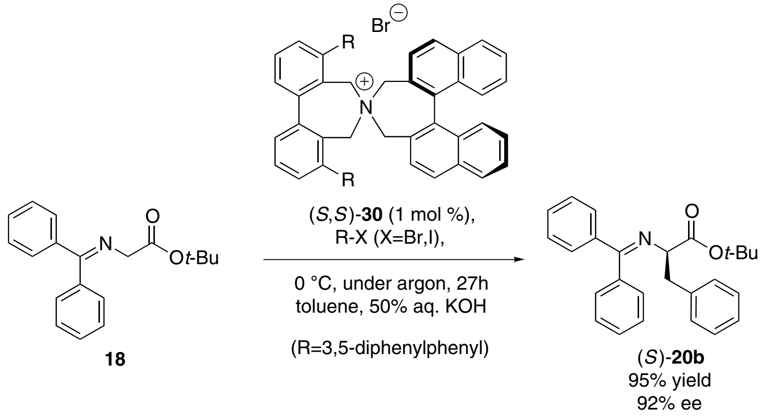


Scheme 3.9

of this structurally rigid spiro ammonium salt as organocatalyst the alkylation proceeds highly enantioselectively with formation of the desired optically active products **20**. The phase-transfer catalyst **29** was preferred for synthesis of a broad range of optically active α-amino acid esters **20**. In the presence of only 1 mol% (*S*,*S*)-**29** high yields of up to 98% and excellent enantioselectivity, often 99% ee, were obtained for the products (*R*)-**20** [34]. Selected examples are summarized in Scheme 3.9. It is worthy of note that the catalyst loading can be reduced to 0.2 mol% without loss of enantiomeric purity. Furthermore, the reaction times are short (0.5 to 10 h) [33, 34]. The reaction rate can be further increased by use of ultrasound, because of the increased reactive interfacial area of the two-phase system under these conditions [35]. The yield and enantioselectivity were comparable with those obtained when the reaction was performed with simple mechanical stirring.

Another advantage of the catalyst **29** is that it enables rational fine-tuning for substrate-specific optimization simply by changing the substitution pattern at the catalyst framework [33, 34]. A current drawback for large scale applications might be access to these impressive catalysts, which are prepared starting from binaphthol in a six-step synthesis.

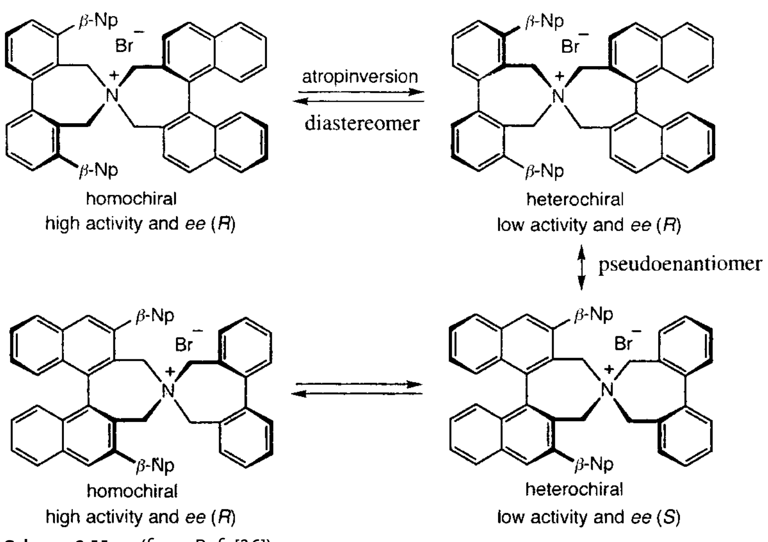
Despite the impressive catalytic properties of **29** (and its analogs), the conformationally rigid *N*-spiro structure can also be a drawback, in particular with regard to conformational adaptation and the difficulty of modification. Addressing this issue,



Scheme 3.10

Maruoka and co-workers developed an elegant solution by creating phase-transfer-catalysts of type **30** [36]. For example, the C_2-symmetric *N*-spiro organocatalyst (*S*,*S*)-**30**, which contains a conformationally flexible biphenyl subunit, efficiently catalyzed the alkylation of glycinate **18** with benzyl bromide, with formation of the product (*R*)-**20b** in 95% yield and with 92% ee (Scheme 3.10) [36].

The high enantioselectivity is because of the substantially different catalytic activity of the diastereomeric homo and hetero isomers, which are in a rapid equilibrium through conformational interconversion. An example of this interconversion, which has been confirmed by experimental studies, is shown in Scheme 3.11 [36]. The catalytically active species, which gives high asymmetric induction, is the

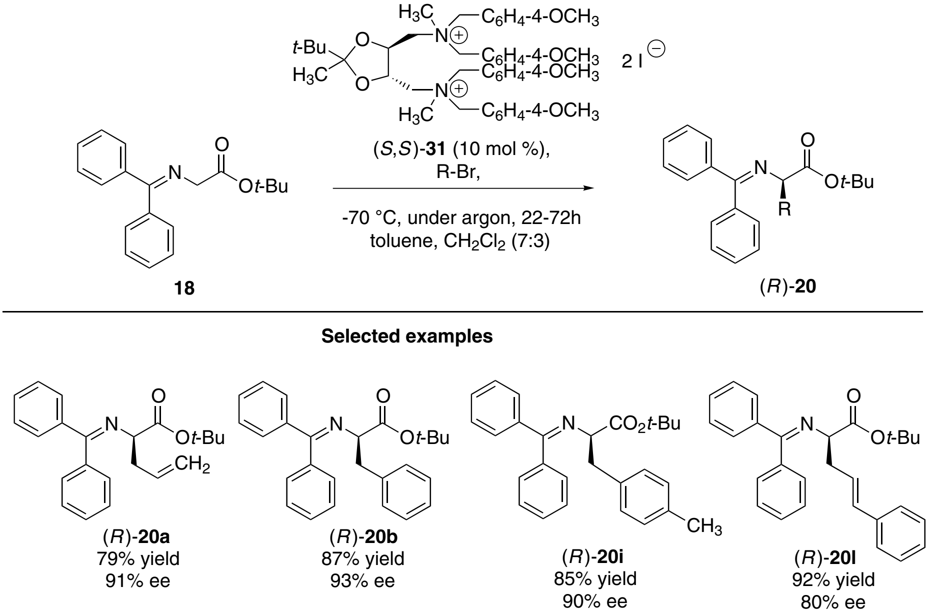


Scheme 3.11 (from Ref. [36])

homochiral form whereas the heterochiral form results in low reactivity and selectivity. These results provide an interesting strategy for molecular design of *N*-spiro catalysts – the requisite chiral information is contained in the binaphthyl subunit whereas the achiral biphenyl structure fulfils the structural requirement needed for fine-tuning of reactivity and enantioselectivity [36].

Very recently, Maruoka and co-workers described a new *N*-spiro quaternary ammonium bromide with two chiral biphenyl structures as easily modifiable subunits [37]. These phase-transfer catalysts with biphenyl subunits, containing methyl groups in the 6,6′-position for inducing chirality, and additionally bulky substituents in the 4-position, efficiently catalyzed the alkylation of protected glycinate with high enantioselectivity of up to 97% ee. The substrate range is broad, for example (substituted) benzyl bromide and allylic and propargylic bromides are tolerated [37].

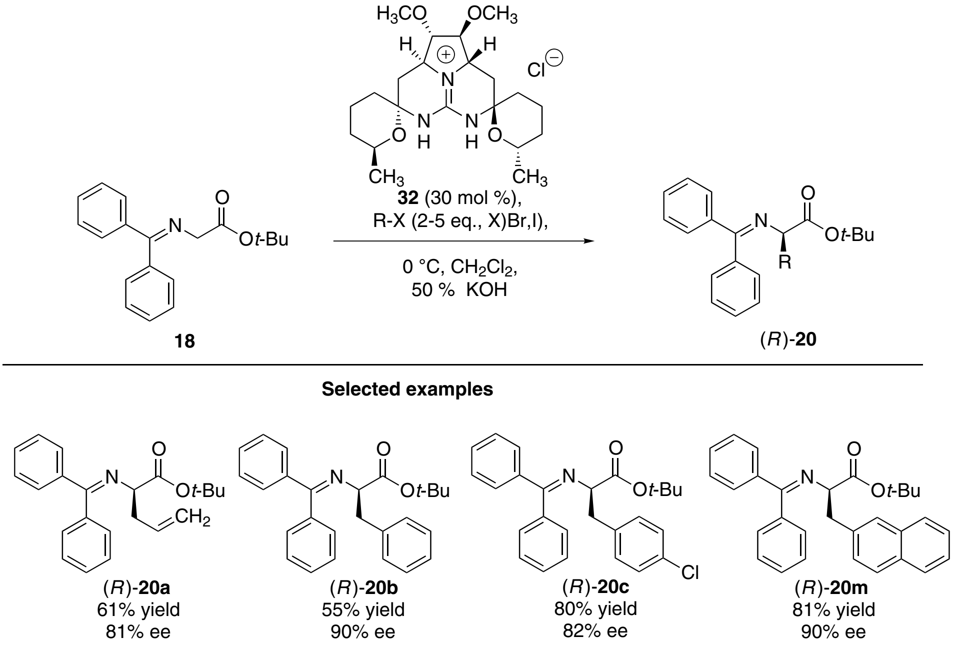
The development of efficient chiral two-center catalysts of type **31** for asymmetric alkylation reactions was recently reported by the Shibasaki group [38–40]. These types of catalyst were designed on the basis of a molecular modeling study, which indicated that the C=N double bond of substrate **18** is fixed between both ammonium cations [38]. To find the optimum catalyst a library of more than 40 new two-center catalysts was screened. For the asymmetric alkylation reaction the tartrate derivative **31** was the best catalyst. Investigation of the substrate range under optimum reaction conditions revealed that high yields (up to 92%) and enantioselectivity (up to 93% ee) were obtained with a broad range of substrates [38]. An overview of the range of substrates is given in Scheme 3.12. For example,



Scheme 3.12

alkylation of **18** with benzyl bromide in the presence of 10 mol% (*S*,*S*)-**31** gave the phenylalanine derivative (*R*)-**20b** in 87% yield and with 93% ee [38]. Irrespective of substitution pattern, *p*-substituted phenylalanine derivatives were obtained with high enantioselectivity in the range 89–91%. Other electrophiles bearing unsaturated carbon–carbon bonds are also suitable substrates, as can be seen, for example, from the successful synthesis of (*R*)-**20l**. The main advantages of these types of two-center catalyst are that both enantiomers can be simply constructed from inexpensive starting materials and easily modified; this is highly desirable for fine-tuning of the catalyst [38].

The Nagasawa group showed that guanidines also are suitable catalysts for asymmetric alkylation processes, and introduced chiral C_2-symmetric pentacyclic guanidines of type **32** as phase-transfer-catalysts [41]. These authors had previously successfully applied this type of catalyst for the hetero Michael reaction [42]. The guanidine **32** was particular efficient in the alkylation reaction. In the presence of 30 mol% **32** asymmetric alkylation of the glycinate derivative **18** proceeds efficiently with formation of the desired products **20** with yields in the range 61–85%, and enantioselectivity in the range 76–90% ee (Scheme 3.13) [41]. For example, the desired α-amino acid ester (*R*)-**20m** was formed in 81% yield and with 90% ee [41]. Recovery of the guanidine catalyst was achieved in almost quantitative yield.



Scheme 3.13

3.2.2
Improving Enantioselectivity During Work-up

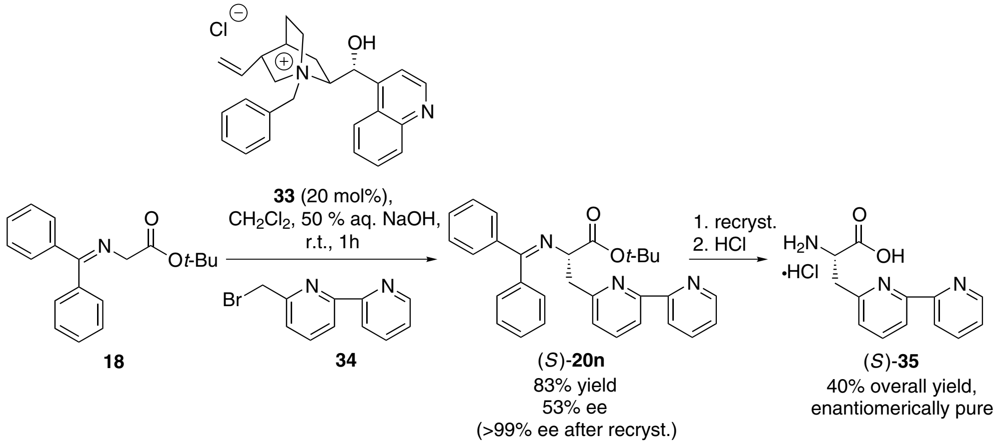
Because of the high potential of alkaloid-based alkylations for synthesis of amino acids, several groups focused on the further enantiomeric enrichment of the products [20]. In addition to product isolation issues, a specific goal of those contributions was improvement of enantioselectivity to ee values of at least 99% ee during downstream-processing (e.g. by crystallization). For pharmaceutical applications high enantioselectivity of >99% ee is required for optically active α-amino acid products.

3.2.3
Specific Application in the Synthesis of Non-natural Amino Acids

Because of its efficiency and broad substrate tolerance with regard to the alkyl halide, organocatalytic asymmetric alkylation has been applied to the synthesis of several unusual amino acids. These non-natural amino acids are often key intermediates in the synthesis of biologically active peptides and other compounds of pharmaceutical importance.

One example is the optically active amino acid derivative (*S*)-**20n** which contains a bipyridyl substituent (Scheme 3.14). The alkylation reaction in the presence of the cinchona alkaloid catalyst **33** proceeds with 53% ee (83% yield of (*S*)-**20n**) and gave the desired enantiomerically pure α-amino acid ester (*S*)-**20n** in >99% ee after re-crystallization [43]. Subsequent hydrolysis of the optically pure (*S*)-**20n** furnished the desired unprotected α-amino acid **35**. A different purification method, subsequent enzymatic resolution, reported by Bowler et al., furnished the α-amino acid product **35** with enantioselectivity of 95% ee [44].

The Imperiali group also reported the preparation of analogous optically active α-amino acids bearing a cyanoanthracene and a substituted pyridyl group, respec-

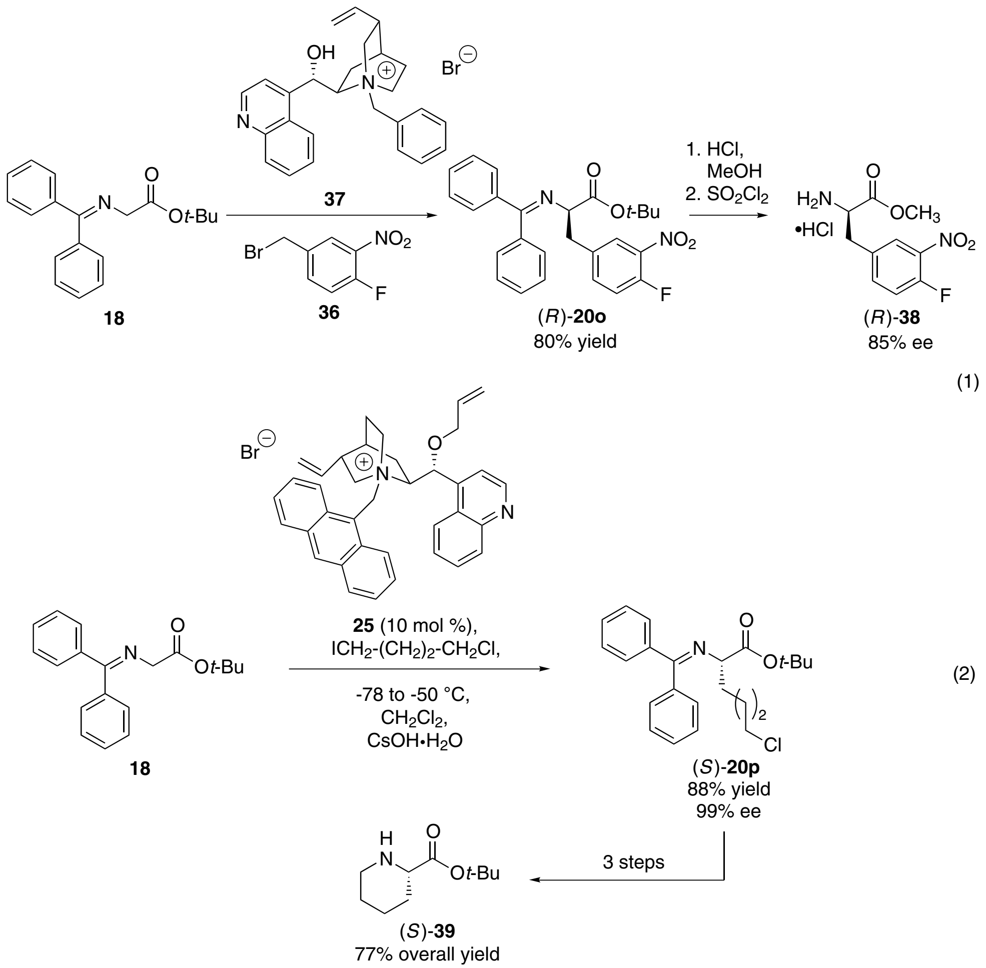


Scheme 3.14

tively [45, 46]. Although asymmetric induction is modest, 52–53% ee, enantiomerically pure samples (> 99% ee) can subsequently be obtained by fractional crystallization.

The synthesis of the methyl ester of (*R*)-4-fluoro-3-nitro-phenylalanine, (*R*)-**38**, a key building block in the preparation of the 16-membered cyclic tripeptide ring system of teicoplanin, was reported by Rao and co-workers [47]. This target molecule **38** was synthesized by means of an asymmetric alkylation reaction in the presence of *N*-benzylcinchoninium bromide (80% yield), followed by hydrolysis and esterification (85% ee; Scheme 3.15; Eq. 1).

The Corey group extended the use of its successful alkylation process, key features of which are the phase-transfer catalyst **25** and solid $CsOH{\cdot}H_2O$ [25], to a key step in the preparation of (*S*)-pipelonic acid ester, **39** (Scheme 3.15; Eq. 2)

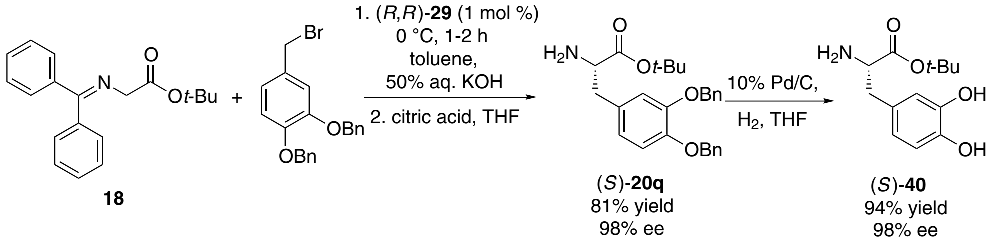


Scheme 3.15

[48]. The catalytic phase-transfer alkylation of **18** with 1-chloro-4-iodobutane afforded the adduct (*S*)-**20l** in 88% yield and excellent 99% ee. Subsequent conversion of this intermediate (*S*)-**20p** into the final product (*S*)-**39** was accomplished in high yield (the overall yield starting from **18** was 77%).

A limitation of the organocatalytic alkylation reaction was, however, discovered by Pirrung et al. when applying the method to the synthesis of (*S*)-*β*-cyclooctatetraenylalanine [49]. Although high yields were obtained, the resulting product was racemic.

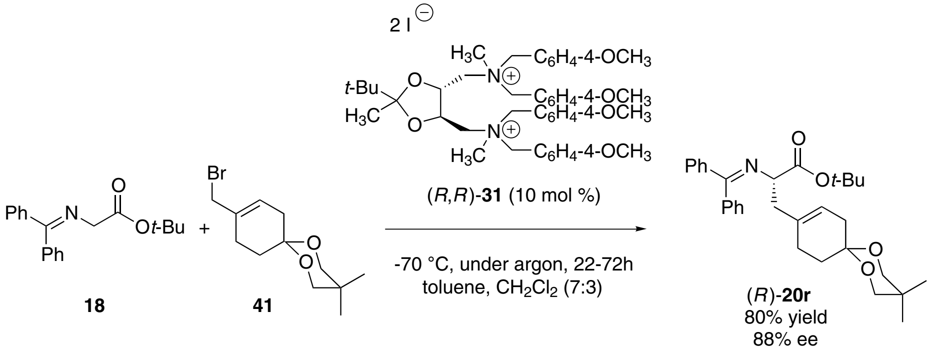
The Maruoka group used their highly enantioselective, structurally rigid, chiral spiro catalysts of type **29** in the synthesis of L-Dopa ester (*S*)-**40** and an analog thereof [50]. Initial asymmetric alkylation in the presence of 1 mol% (*R*,*R*)-**29** gave the intermediate (*S*)-**20q** in 81% yield and 98% ee (Scheme 3.16). Subsequent debenzylation provided the desired L-Dopa ester (*S*)-**40** in 94% yield and 98% ee. This reaction has also already been performed on a gram-scale. The Maruoka group also reported the application of the chiral phase-transfer catalyst (*R*,*R*)-**29** for synthesis of a variety of 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid derivatives; these also were formed with high enantioselectivity [51].



Scheme 3.16

The Maruoka group have reported further application of *N*-spiro phase-transfer catalysts of type **29** to the diastereoselective α-alkylation of *N*-terminal di-, tri-, and tetrapeptides [52]. The reactions proceed with high diastereoselectivity, furnishing a diastereomeric ratio (d.r.) of up to 99:1 for the resulting dipeptide products.

Very recently the Shibasaki group extended the range of application of their asymmetric two-center catalysts **31** to the synthesis of amino acid derivative intermediates for aeruginosin 298-A and analogs thereof [39]. Aeruginosin has a tetrapeptide-like structure and contains non-standard α-amino acids. The synthesis of the key intermediate (*S*)-**20r**, bearing a bulky substituent, is shown in Scheme 3.17 [39]. In the presence of the catalyst (*R*,*R*)-**31** the desired amino acid derivative (*S*)-**20r** was obtained in 80% yield and with 88% ee [39]. The catalyst **31**, which is very stable under basic conditions, could be recovered in 80–90% yield and re-used efficiently [39].

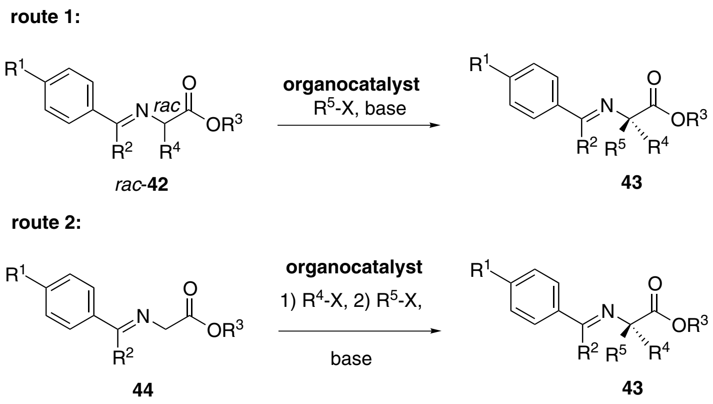


Scheme 3.17

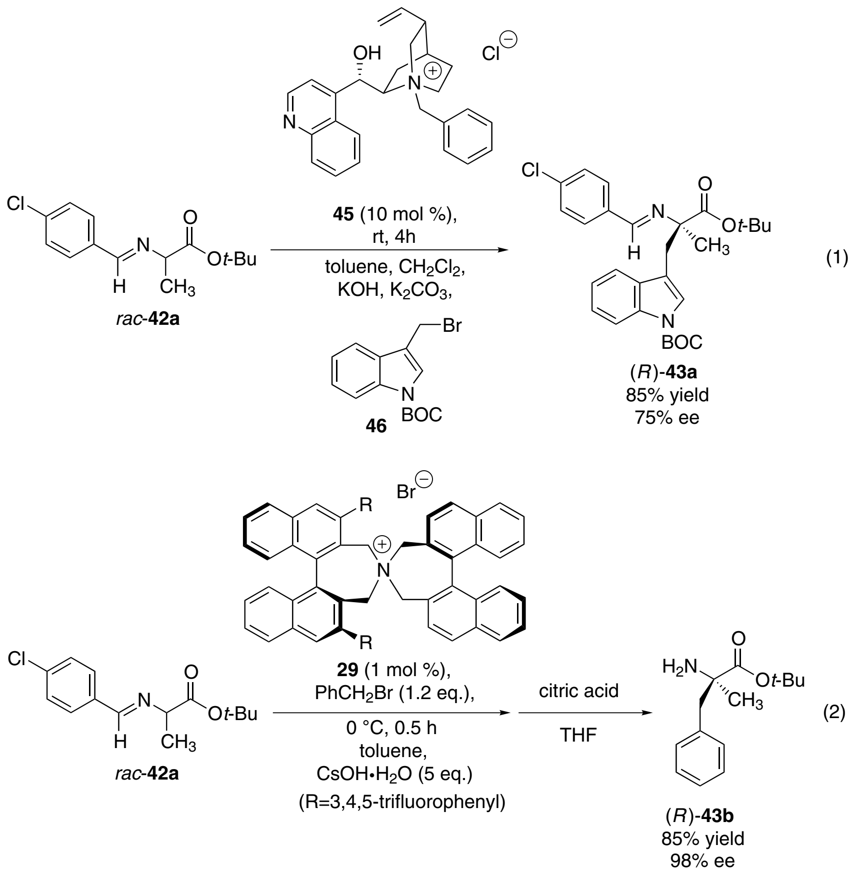
3.2.4
Synthesis of α,α-Dialkylated Amino Acids

Besides the "typical" monoalkylated α-amino acids, the related non-proteinogenic α,α-disubstituted analogs are becoming increasingly important because of their role in the design of special pharmaceutically interesting peptides [53]. The range of suitable catalytic processes for their preparation is, however, limited [54, 55]. As an attractive catalytic route, organocatalytic asymmetric alkylation using phase-transfer catalysts was found to be very efficient. Two principle routes are available for application of this organocatalytic concept; they are shown in Scheme 3.18.

In route 1 a racemate, *rac*-**42**, is used as the starting material. Deprotonation and enantioselective alkylation of the resulting enolate give the desired products of type **43**. The alternative, second route is based on use of the glycinate **44** as starting material. Alkylation steps with different alkyl halides furnish the desired product **43**.



Scheme 3.18

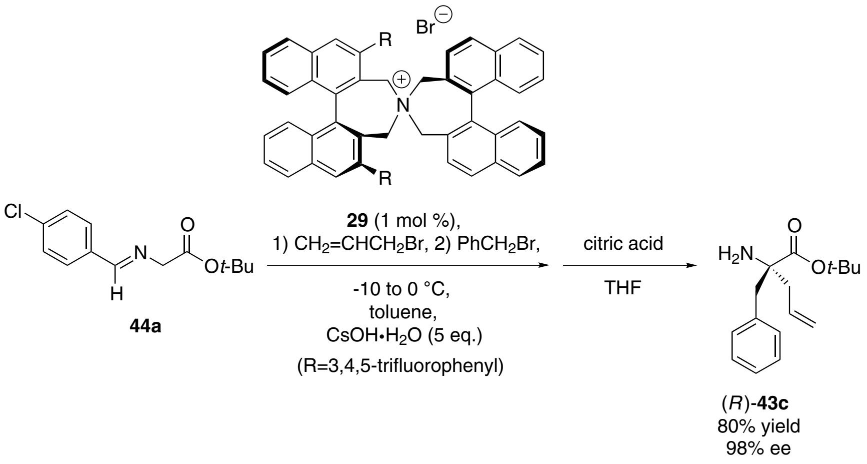


Scheme 3.19

The successful conversion of a racemic amino acid derivative into an optically active α,α-disubstituted amino acid derivative, in accordance with Scheme 3.18, route 1, has been reported by the O'Donnell group [56]. A representative example is given in Scheme 3.19, Eq. (1). An alanine derivative, *rac*-**42a**, is converted into the dialkylated product (*R*)-**43a** in 85% yield and with 75% ee. The reaction proceeds *via* solid–liquid phase-transfer catalysis. It should be added that analogous reactions were also performed starting from enantiomerically pure amino acids [57]. The enantioselective PTC-alkylation starting from racemates can be also achieved very efficiently when using the ammonium salt catalyst, **29**, developed by Maruoka and co-workers (Scheme 3.19, Eq. 2) [58]. The benzylation of the alanine derivative *rac*-**42a** gave the desired benzylated alanine derivative (*R*)-**43b** in 85% yield and with 98% ee. The analogous benzylation reaction with either D- or L-alanine-derived imine gave almost the same results. The reaction has broad generality, and gave the dialkylated products of type **43** in yields of 60–85% and enantioselectivity of 91–99% ee.

A related approach has recently been reported by Belokon and Kagan et al. These workers used chiral TADDOL-type diols, derived from tartaric acid and 2-amino-2′-hydroxy-1,1′-binaphthyl (NOBIN), as catalysts to obtain yields of up to 95% and enantioselectivity up to 93% ee [59–61]. The catalytically active species seem to be the sodium salts of the diols.

The Maruoka group recently reported an alternative concept based on a one-pot double alkylation of the aldimine of glycine butyl ester, **44a**, in the presence of the chiral ammonium salt **29** as chiral phase-transfer catalyst (the principal concept of this reaction is illustrated in Scheme 3.18, route 2) [58]. Under optimized reaction conditions products of type **43** were obtained in yields of up to 80% and with high enantioselectivity (up to 98% ee). A selected example is shown in Scheme 3.20.

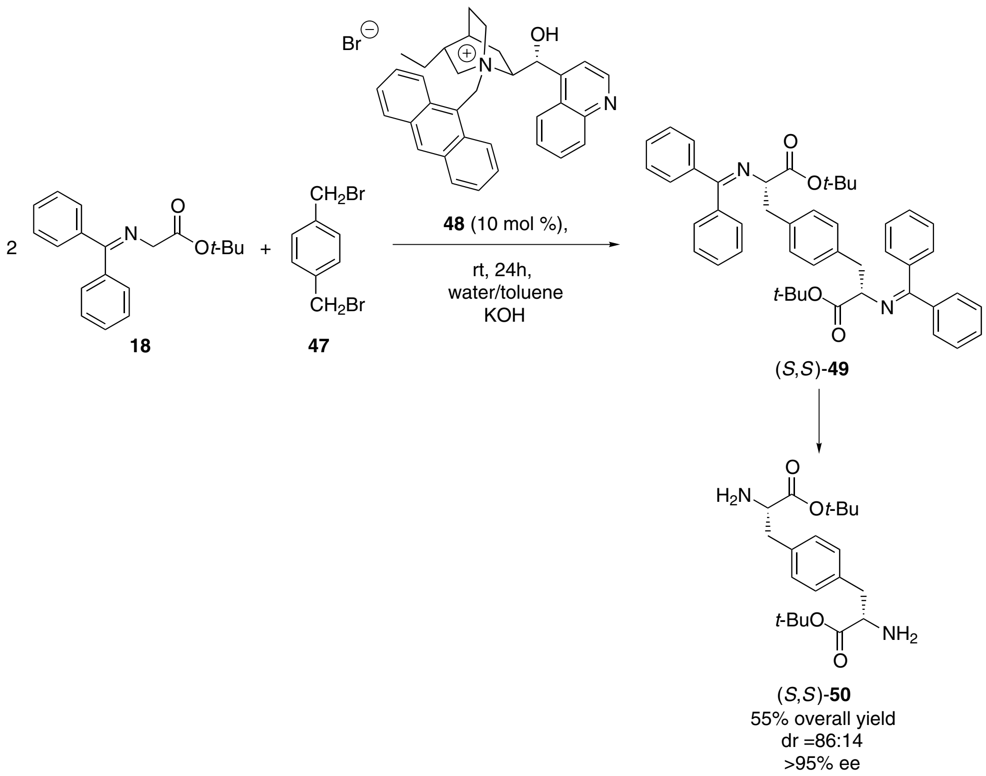


Scheme 3.20

The presence of the 3,4,5-trifluorosubstituted phenyl substituent at the 3,3′-position of the binaphthyl framework is beneficial for high enantioselectivity. The stereochemistry of the newly created stereogenic quaternary carbon center was apparently determined in the second alkylation step. This bisalkylation method starting from readily available glycinate ester **44** seems to be particularly beneficial when an access to racemates of type **42** as starting materials is difficult. The Maruoka group has also reported the alkylation of an alanine derivative in the presence of a new *N*-spiro chiral quaternary ammonium bromide designed from optically active 4,6-disubstituted biphenyl subunits [37]. This reaction proceeds with high enantioselectivity (95% ee).

3.2.5
Enantio- and Diastereoselective Processes – Synthesis of α-Amino Acid Derivatives with Two Stereogenic Centers

The use of chiral phase-transfer-based alkylation in the asymmetric synthesis of bis-α-amino acid esters has been described by the Lygo group. When the dibromide

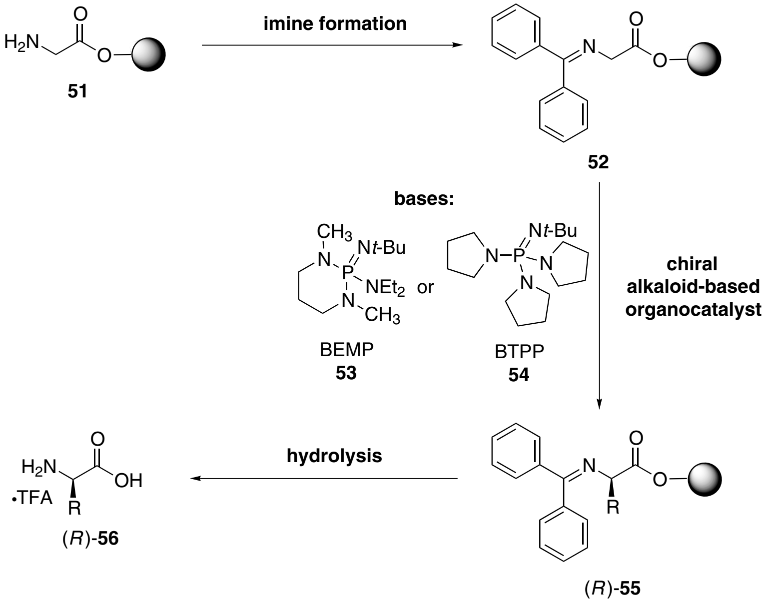


Scheme 3.21

47 (0.5 equiv.) and glycinate **18** (1 equiv.) were reacted in the presence of the cinchonidinium derivative **48** as organocatalyst (10 mol%), enantio- and diastereoselective alkylation and subsequent hydrolysis furnished the desired product (*S*,*S*)-**50** in 55% overall yield, a d.r. of 86:14, and enantioselectivity of ≥95% ee (Scheme 3.21) [62]. This reaction also works with other types of dibromide substrate. In those reactions enantioselectivity ≥ 95% was obtained accompanied by a diastereomeric ratio of up to 91:9. The syntheses of dityrosine and isodityrosine by means of this alkylation methodology is also reported to proceed with high enantioselectivity and diastereoselectivity [63].

3.2.6
Solid-phase Syntheses

The solid-phase synthesis of α-amino acids *via* alkaloid-catalyzed alkylation has been investigated by the O'Donnell group [64, 65]. The solid-phase based synthetic approach is particularly useful for rapid preparation of α-amino acids for combinatorial application. The concept of this solid-phase synthetic approach, which comprises three key steps, is shown in Scheme 3.22 (for formation of (*R*) enantiomers). First, solid-phase bound glycine, **51**, is converted into its benzophenone imine de-



Scheme 3.22

rivative **52**. Subsequent asymmetric alkylation furnishes the desired optically active α-amino acid derivative of type **55**. Hydrolysis with formation of the "free", *N*-non-protected polymer-bound amino acid **56** is the final step. Polymer-bound amino acids of type **55** are of interest for a wide variety of combinatorial applications.

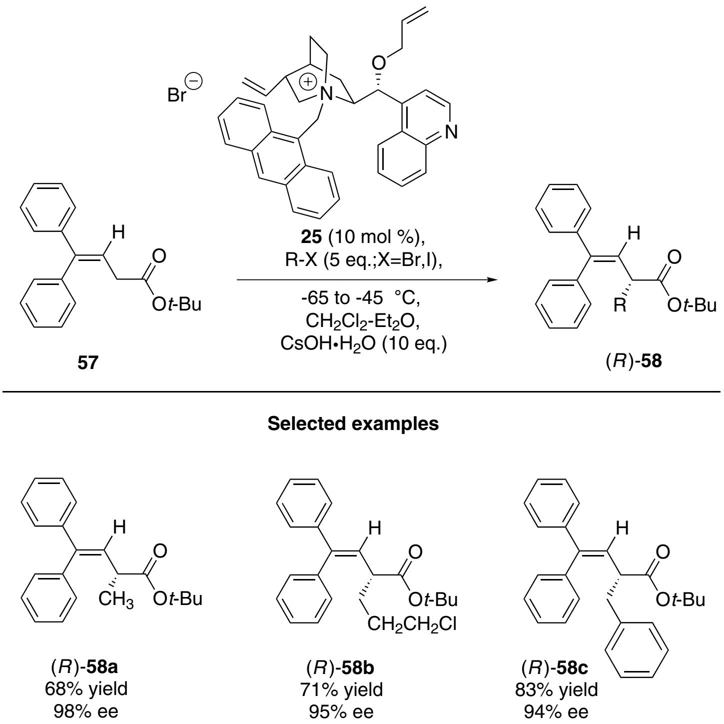
A characteristic feature of this solid-phase amino acid synthesis is the use of the phosphazene bases **53** and **54** for the PTC alkylation reaction [64, 65]. Because these compounds, which are soluble in organic media, do not react with alkyl halides, both alkyl halide and phosphazene bases can be added together at the start of the reaction, which is useful practically [65]. Cinchonine and cinchonidine-derived salts, e.g. **25**, were found to be very efficient catalysts. Under optimum conditions the alkylation proceeds with enantioselectivity in the range 51–99% ee, depending on the alkyl halide component [65]. Seventeen different alkyl halides were tested. After subsequent hydrolysis with trifluoroacetic acid the corresponding free amino acids were obtained in high yield (often >90%).

This methodology has, therefore, reached a high level of efficiency and is a valuable tool for rapid preparation of optically active α-amino acids and related derivatives.

The use of Merrifield resin-bound alkaloid-based organocatalysts has also been reported [66–67]. The best results were obtained when attachment to the Merrifield resin was made *via* the hydroxy moiety of a (cinchonidine) alkaloid derivative [67]. The immobilization of alkaloid-derived catalysts on poly(ethylenglycol) (and modifications thereof) was also developed [68a, b]. Furthermore, asymmetric catalytic alkylations under micellar conditions were reported [68c].

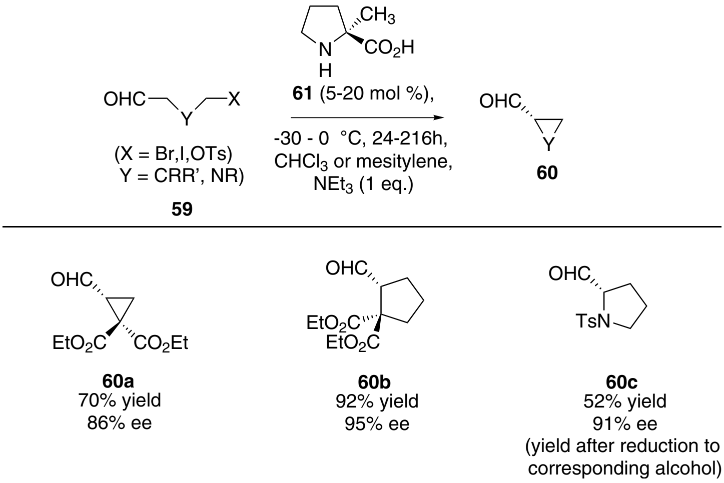
3.3
α-Alkylation of Other Acyclic Substrates

Besides the glycinate ester derivatives described above, other types of enolate-forming compounds have proved to be useful substrates for enantioselective alkylation reactions in the presence of cinchona alkaloids as chiral PTC catalysts. The Corey group reported the alkylation of enolizable carboxylic acid esters of type **57** in the presence of **25** as organocatalyst [69]. The alkylations furnished the desired α-substituted carboxylate **58** in yields of up to 83% and enantioselectivity up to 98% ee (Scheme 3.23). It should be added that high enantioselectivity in the range 94–98% ee was obtained with a broad variety of alkyl halides as alkylation agents. The product **58c** is a versatile intermediate in the synthesis of an optically active tetrahydropyran.



Scheme 3.23

Very recently, the first catalytic asymmetric intramolecular α-alkylation of an aldehyde has been achieved by the List group [70]. In the presence of α-methyl-substituted *L*-proline, (*S*)-**61**, as organocatalyst, ring-forming reactions leading to chiral cyclopentanes, cyclopropanes, and pyrrolidines proceed with high enantioselectivity – in the range 86–96% ee. Selected examples are shown in Scheme



Scheme 3.24

3.24. The cyclopentane derivative **60b** was obtained in both high yield (92%), and enantioselectivity (95% ee). Interestingly, lower yield (80%) and enantioselectivity (68% ee) were obtained when *L*-proline was used as a catalyst instead of (*S*)-**61**, showing the beneficial effect of the methyl-substituent at the α-position on catalytic efficiency.

3.4
Fluorination, Chlorination, and Bromination Reactions

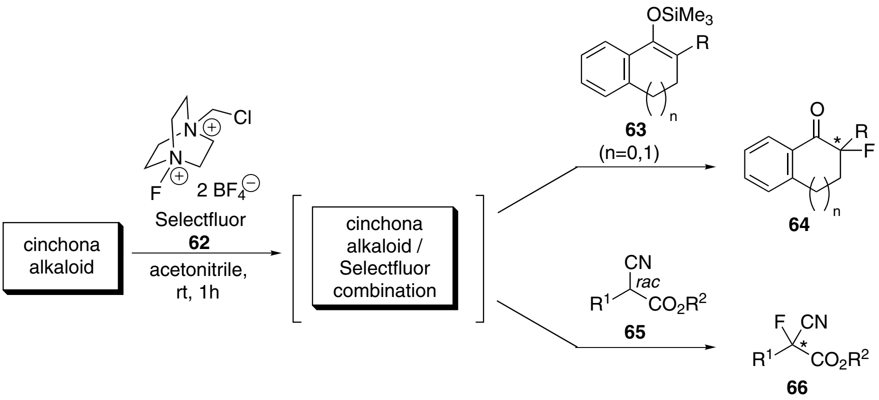
The halogenation of alkane C–H bonds plays an important role in organic synthesis [71]. Numerous industrial examples of halogenated products are known with a broad range of applications in the fields of fine and specialty chemicals and the life science industry. Although most commercially important halogenations are non-asymmetric reactions, the development of methods for enantioselective C–X formations (X = F, Cl, Br) has gained increasing interest. In recent work organocatalytic syntheses have been shown to be versatile tools.

3.4.1
Fluorination Reactions

A wide range of fluorinated compounds are applied as pharmaceuticals and agrochemicals. Several stereoselective methods are used for synthesis of optically active molecules bearing a C–F bond at the stereogenic carbon atom [72, 73]. These are mainly based on diastereoselective fluorination of chiral molecules or enantioselective alkylation of fluoroorganic compounds. Asymmetric introduction of a fluorine

moiety is an alternative [74–77], e.g. *via* chiral sulfonamide-type fluorinating reagents. This method is, however, based on use of multistep procedures for preparation of the *N*-fluorinated reagents. Low chemical yield and optical purity are also obtained in fluorination reactions.

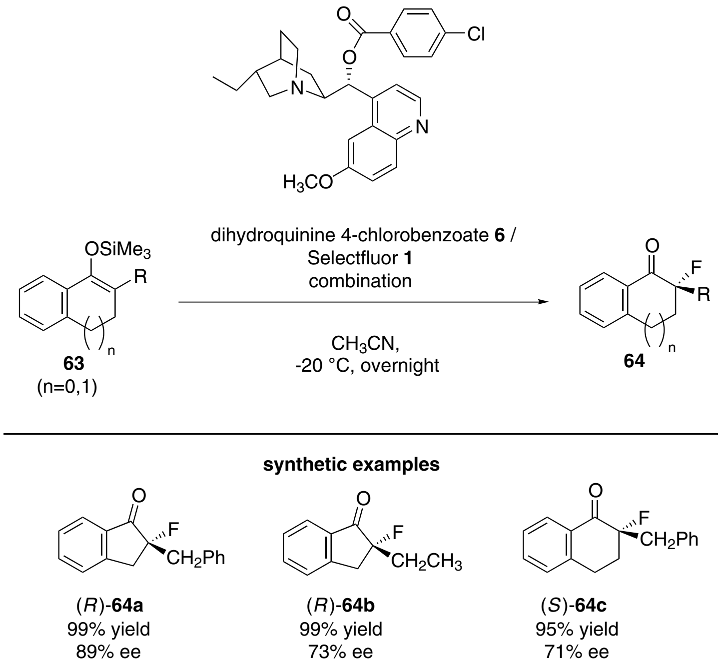
An enantioselective fluorination method with catalytic potential has not been realized until recently, when Takeuchi and Shibata and co-workers and the Cahard group independently demonstrated that asymmetric organocatalysis might be a suitable tool for catalytic enantioselective construction of C–F bonds [78–80]. This agent-controlled enantioselective fluorination concept, which requires the use of silyl enol ethers, **63**, or active esters, e.g. **65**, as starting material, is shown in Scheme 3.25. Cinchona alkaloids were found to be useful, re-usable organocatalysts, although stoichiometric amounts were required.



Scheme 3.25

The Takeuchi and Shibata group achieved successful asymmetric fluorination of silyl enol ethers and acyclic esters by using a preformed combination of Selectfluor, **62**, and cinchona alkaloid derivatives as an efficient fluorinating agent [78, 79]. This combination is simply prepared by mixing a solution of the cinchona alkaloid and Selectfluor for 1 h in acetonitrile in the presence of a molecular sieve. The fluorination of silyl enol ethers **63** proceeds efficiently in acetonitrile at −20 °C. Dihydroquinine 4-chlorobenzoate, **67**, was the preferred cinchona alkaloid. The desired fluorinated products, **64**, were obtained in high yields (71 to 99%) and good enantioselectivity (up to 89% ee) [78, 79]. Some representative examples are shown in Scheme 3.26. Slightly increased enantioselectivity was observed when the reaction was performed at −80 °C ((*R*)-**64a** 91% ee compared with 89% ee at −20 °C). The yield, however, was somewhat lower (yield of (*R*)-**64a** 86% compared with 99% at −20 °C).

This method is also useful for enantioselective fluorination of alkyl esters of type **65** (Scheme 3.27, Eq. 1) [78, 79]. The resulting fluoro-organic products **66** are use-

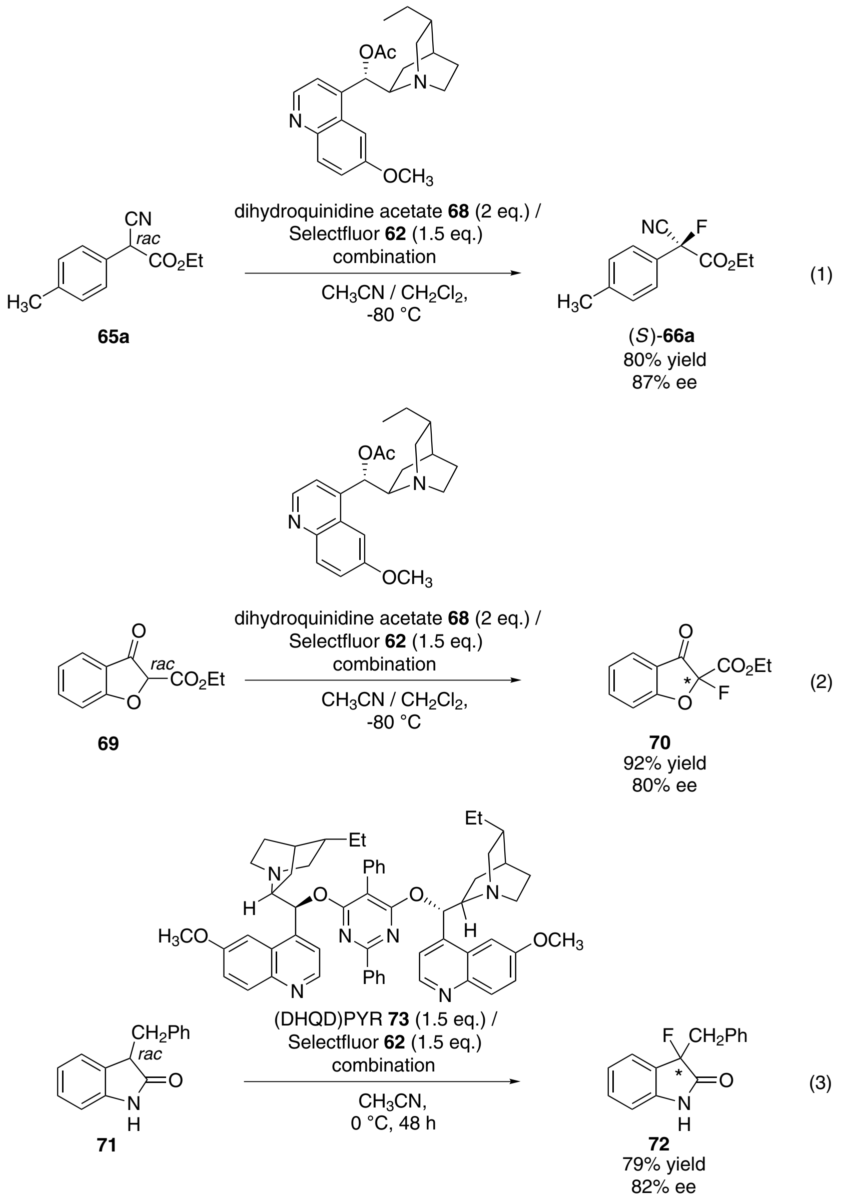


Scheme 3.26

ful compounds, e.g. as chiral derivatizing agents. The reaction was particularly challenging, because a racemic substrate, **65**, must be converted enantioselectively into the desired product, **66**. This is achieved by means of alkaloid base-catalyzed deprotonation before the fluorination step. For this reaction, dihydroquinidine derivatives, e.g. **68**, were found to be the most efficient organocatalysts. The reaction is conducted at a somewhat lower reaction temperature and led to the desired products **66** in high yields (80–92%). Enantioselectivity was in the range 76–87% ee. As a selected example, the enantioselective fluorination of α-cyano-α-tolyl acetate, **65a**, gave the organofluorine compound **66a** in 80% yield and 87% ee (Scheme 3.27, Eq. 1). The alkaloid base can be recovered and successfully re-used in the fluorination reaction.

Interestingly, cyclic β-keto esters, e.g. **69**, can be also fluorinated with enantioselectivity up to 80% ee, although the yield and enantioselectivity depend strongly on the type of substrate. A representative example of asymmetric fluorination of a cyclic ester is shown in Scheme 3.27, Eq. (2). In addition, oxindoles **71** have been successfully fluorinated, as shown in Scheme 3.27, Eq. (3). Under optimized conditions, the desired 3-substituted 3-fluorooxindole, **72**, was obtained in 79% yield and with enantioselectivity of 82% ee.

It is worthy of note that this practical fluorination method developed by Takeuchi and Shibata et al. is based on the use of commercially available reagents. In addi-



Scheme 3.27

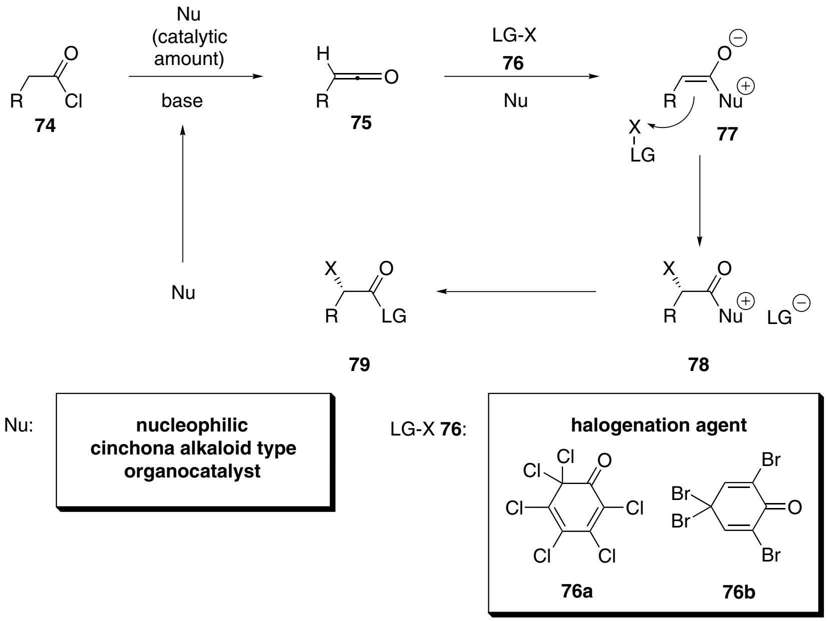
tion, the *in situ* preparation of the fluorinating agent without the need for isolation is advantageous, and might be the basis of a process with catalytic amount of the alkaloid base in the future. In a mechanistic study it has been shown that *N*-fluorochinchona alkaloids are the reactive intermediates [79].

A related approach was recently reported by the Cahard group, who used preformed *N*-fluoro ammonium salts of cinchona alkaloids as fluorinating agents [80–82]. These salts were prepared, as described above, from a cinchona alkaloid and Selectfluor in acetonitrile. The *N*-fluoro alkaloid salt with tetrafluoroborate as anion were, however, isolated and purified (rather than being used *in situ*), and the reaction conditions were slightly different. C–F bond formation proceeds well and high yields (up to 98%) were obtained. Compared with the procedure developed by Takeuchi and Shibata et al., however, enantioselectivity was somewhat lower – in the moderate range 36–56% ee when sodium enolates were used as substrates [80]. Use of *N*-phthaloylglycine derivatives as starting materials, however, afforded the corresponding α-fluorinated products in yields of up to 91% and enantioselectivity up to 94% ee [82].

In summary, these procedures for asymmetric formation of C–F bonds are efficient but still require use of stoichiometric amounts of organocatalyst. Thus, an extension of this process toward catalytic synthesis with reduced "catalytic amounts" of alkaloids is highly desirable.

3.4.2
Chlorination and Bromination Reactions

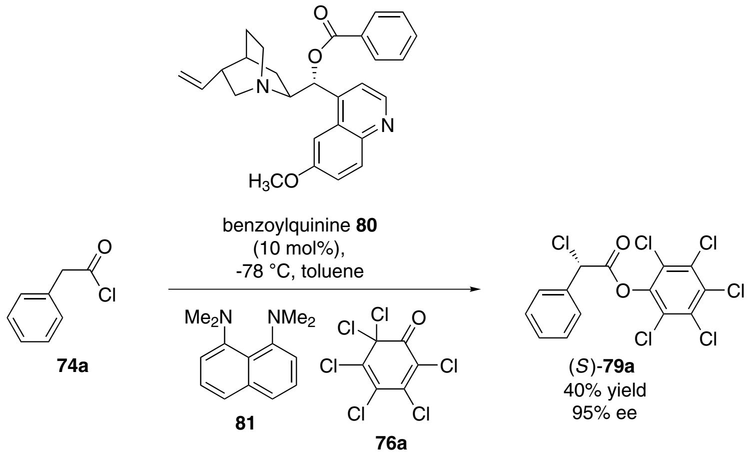
A similar catalytic procedure for enantioselective formation of C–Br and C–Cl bonds has been reported recently by the Lectka group [83]. The concept of this α-halogenation of carbonyl compounds is tandem asymmetric halogenation and esterification (Scheme 3.28). Inexpensive acyl halides, **74**, are used as starting



Scheme 3.28

materials and cinchona alkaloids are suitable organocatalysts. In the first step the chiral alkaloid base reacts with the *in-situ*-generated ketenes **75** under formation of zwitterionic enolates, **77**. These intermediates are subsequently converted, with an electrophilic halogen **76**, into the desired products, **79**.

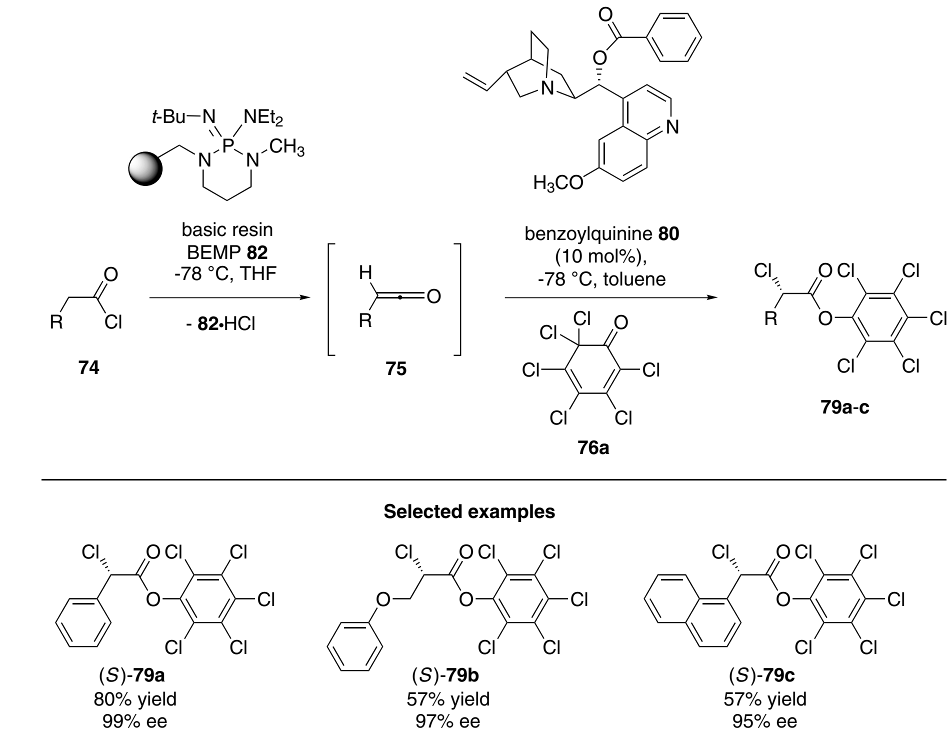
The choice of halogenation agent was found to be important. Initial screening of different chlorination agents revealed that the electrophilic perchlorocyclohexadienone, **76a**, is particularly useful. For example, conversion of **74a** with **76a** gave the α-chlorinated compound **79a** with high enantioselectivity (95% ee), although the conversion was limited (40% yield) because of significant side reactions (Scheme 3.29) [83a].



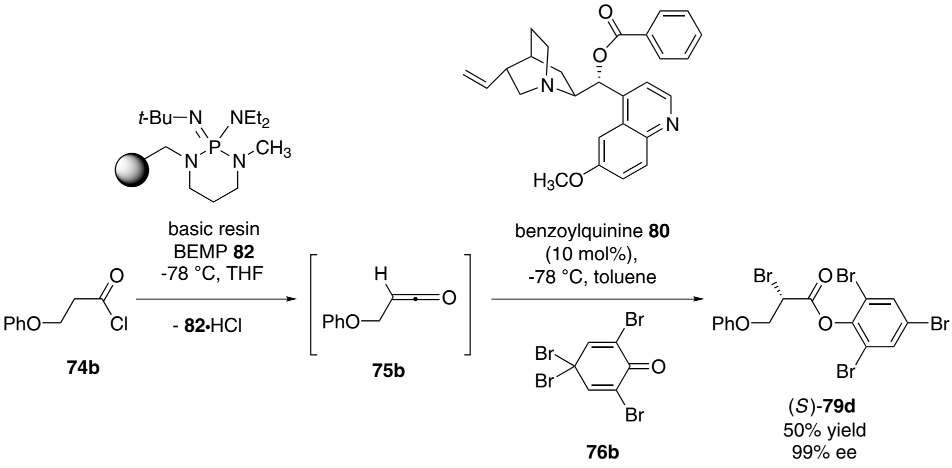
Scheme 3.29

A breakthrough resulting in high yields was achieved when another method of ketene formation using the basic solid-phase-bound BEMP, **82**, was applied (Scheme 3.30) [83a]. In the first step the ketenes are formed rapidly and quantitatively by passing a solution of **74** in THF through the basic resin **82**. In a subsequent step the ketene intermediates react enantioselectively after addition of an organocatalyst (10 mol%) and the chlorination agent **76a**. By use of these reaction conditions the product **79a** was obtained in remarkably increased yield (80%) and with excellent enantioselectivity (99% ee). Several other substrates were also investigated and satisfactory yields and excellent enantioselectivity (up to 99% ee) were usually obtained. Selected examples are surveyed graphically in Scheme 3.30. It is worthy of note, however, that the reaction employing a solid-phase catalyst of resin-bound quinine failed, apparently because of rapid deactivation of the catalyst [83a]. Further improvements of this catalytic asymmetric α-chlorination of acid halides have been reported very recently by the Lectka group also [83b].

This type of reaction is not limited to chlorination but can be extended to bromination reactions also. In a preliminary study it was found that reaction of brominating agent **76b** provided the α-bromo compound **79d** in 50% and with excellent



Scheme 3.30



Scheme 3.31

enantioselectivity (99% ee; Scheme 3.31) [83]. The catalyst used was 10 mol% benzoylquinine, **80**.

Furthermore, two efficient methods for a direct catalytic asymmetric α-chlorination of aldehydes have been developed very recently [84, 85]. The MacMillan group successfully used a chiral imidazolidinone as organocatalyst with a typical catalytic amount of 5 mol% in combination with **76a** as chlorinating agent [84]. In addition, the Jørgensen group found that α-chlorination of aldehydes proceeds enantioselectively when using *L*-proline amide and (2*R*, 5*R*)-diphenylpyrrolidine as organocatalysts and NCS as the chlorinating agent [85].

Conclusion

The asymmetric alkylation of cyclic ketones, imines of glycine esters, and achiral, enolizable carbonyl compounds in the presence of chiral phase-transfer organocatalysts is an efficient method for the preparation of a broad variety of interesting compounds in the optically active form. The reactions are not only highly efficient, as has been shown impressively by, e.g., the synthesis of enantiomerically pure α-amino acids, but also employ readily available and inexpensive catalysts. This makes enantioselective alkylation *via* chiral phase-transfer catalysts attractive for large-scale applications also. A broad range of highly efficient chiral phase-transfer catalysts is also available.

In addition, enantioselective fluorination, chlorination, and bromination reactions enable easy formation of C–X bonds (X = F, Cl, Br) under mild reaction conditions. This synthesis is also a proof that halogenation reactions can be conducted with high stereocontrol. All organocatalytic halogenations yet reported are α-halogenations of carbonyl compounds. A future challenge will certainly be to discover more general halogenation routes, in particular halogenation other substrates.

References

1 For excellent reviews, see: (a) M. J. O'Donnell in: *Catalytic Asymmetric Synthesis* (Ed.: I. Ojima), 2nd ed., Wiley–VCH, Weinheim, **2000**, chapter 10; (b) A. Nelson, *Angew. Chem.* **1999**, *111*, 1685–1687; *Angew. Chem. Int. Ed.* **1999**, *38*, 1583–1585; (c) T. Shiori, S. Arai in: *Stimulating Concepts in Chemistry* (Eds.: F. Vögtle, J. F. Stoddart, M. Shibasaki), John Wiley and Sons, New York, **2000**, p. 123–143. (d) M. J. O'Donnell, *Acc. Chem. Res.* **2004**, *37*, 506–517; (e) K. Maruoka, T. Ooi, *Chem. Rev.* **2003**, *103*, 3013–3028.

2 N. Furukawa, Y. Sugihara, H. Fujihara, *J. Org. Chem.* **1989**, *54*, 4222–4224.

3 U.-H. Dolling, P. Davis, E. J. J. Grabowski, *J. Am. Chem. Soc.* **1984**, *106*, 446–447.

4 Previous attempts of enantioselective alkylations of carbanions via phase-transfer catalysis were reported but

resulted in low enantioselectivity of <10% ee. For selected earlier examples, see: (a) S. Julia, A. Ginebreda, J. Guixer, *J. Chem. Soc., Chem. Commun.* **1978**, 742–743; (b) S. Julia, A. Ginebreda, J. Guixer, A. Thomas, *Tetrahedron Lett.* **1980**, 3709–3712; (c) S. Julia, A. Ginebreda, J. Guixer, J. Masana, A. Thomas, S. Colonna, *J. Chem. Soc., Perkin Trans 1* **1981**, 574–577.
5 D. L. Hughes, U.-H. Dolling, K. M. Ryan, E. F. Schoenewaldt, E. J. J. Grabowski, *J. Org. Chem.* **1987**, *52*, 4745–4752.
6 A. Bhattacharya, U.-H. Dolling, E. J. J. Grabowski, S. Karady, K. M. Ryan, L. M. Weinstock, *Angew. Chem.* **1986**, *98*, 442–443; *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 476–477.
7 T. B. K. Lee, G. S. K. Wong, *J. Org. Chem.* **1991**, *56*, 872–875.
8 R. S. E. Conn, A. V. Lovell, S. Karady, L. M. Weinstock, *J. Org. Chem.* **1986**, *51*, 4710–4711.
9 M. Masui, A. Ando, T. Shioiri, *Tetrahedron Lett.* **1988**, 2835–2838.
10 W. Nerinckx, M. Vandewalle, *Tetrahedron: Asymmetry* **1990**, *1*, 265–267.
11 J. J. Eddine, M. Cherqaoui, *Tetrahedron: Asymmetry* **1995**, *6*, 1225–1228.
12 V. L. K. Valli, G. V. M. Sarma, B. M. Choudary, *Ind. J. Chem.* **1990**, *29B*, 481–482.
13 J. M. McIntosh, S. O. Acquaah, *Can. J. Chem.* **1988**, *66*, 1752–1756.
14 K. Manabe, *Tetrahedron Lett.* **1998**, *39*, 5807–5810.
15 A. Solladie-Cavallo, A. Diep-Vohuule, V. Sunjic, V. Vinkovic, *Tetrahedron: Asymmetry* **1996**, *7*, 1783–1788.
16 A.-H. Li, L.-X. Dai, X.-L. Hou, Y.-Z. Huang, F.-W. Li, *J. Org. Chem.* **1996**, *61*, 489–493.
17 K. Julienne, P. Metzner, *J. Org. Chem.* **1998**, *63*, 4532–4534.
18 T. Saito, D. Akiba, M. Sakairi, S. Kanazawa, *Tetrahedron Lett.* **2001**, *42*, 57–59.
19 For some references describing the synthesis of these substrates, see: (a) M. J. O'Donnell, R. L. Polt, *J. Org. Chem.* **1982**, *47*, 2663–2666; (b) M. J. O'Donnell in: *Encyclopedia of Reagents for Organic Synthesis* (Ed.: L. Paquette), Vol. 4, **1995**, John Wiley, Chichester, p. 2435 f.
20 For an excellent recent review about this reaction, see: M. J. O'Donnell, *Aldrichim. Acta* **2001**, *34*, 3–15.
21 M. J. O'Donnell, W. D. Bennett, S. Wu, *J. Am. Chem. Soc.* **1989**, *111*, 2353–2355.
22 M. J. O'Donnell, S. Wu, J. C. Huffman, *Tetrahedron* **1994**, *50*, 4507–4518.
23 M. J. O'Donnell, S. Wu, I. Esikova, A. Mi, US Pat. 5554753, **1996**; *Chem. Abstr.* **1995**, *123*, 9924.
24 For a theoretical study on the mechanism, see: K. B. Lipkowitz, M. W. Cavanaugh, B. Baker, M. J. O'Donnell, *J. Org. Chem.* **1991**, *56*, 5181–5192.
25 (a) E. J. Corey, F. Xu, M. C. Noe, *J. Am. Chem. Soc.* **1997**, *119*, 12414–12415; (b) For preparation of the catalyst, see: E. J. Corey, M. C. Noe, *Org. Synth.* **2003**, *80*, 38–45.
26 B. Lygo, P. G. Wainwright, *Tetrahedron Lett.* **1997**, *49*, 8595–9598.
27 (a) B. Lygo, J. Crosby, T. R. Lowdon, P. G. Wainwright, *Tetrahedron Lett.* **1997**, *38*, 2343–2346; (b) B. Lygo, B. I. Andrews, J. Crasby, J. A. Peterson, *Tetrahedron Lett.* **2002**, *43*, 8015–8018; (c) B. Lygo, B. Allbutt, S. R. James, *Tetrahedron Lett.* **2003**, *44*, 5629–5632.
28 E. J. Corey, M. C. Noe, *J. Am. Chem. Soc.* **1996**, *118*, 11038–11053.
29 H.-g. Park, B.-S. Jeong, M.-S. Yoo, J.-H. Lee, M.-k. Park, Y.-J. Lee, M.-J. Kim, S.-s. Jew, *Angew. Chem.* **2002**, *114*, 3162–3164; *Angew. Chem. Int. Ed.* **2002**, *41*, 3036–3038.
30 S.-s. Jew, B.-S. Jeong, M.-S. Yoo, H. Huh, H.-g. Park, *Chem. Commun.* **2001**, 1244–1245.
31 H.-g. Park, B.-S. Jeong, M.-S. Yoo, M.-k. Park, H. Huh, S.-s. Jew, *Tetrahedron Lett.* **2001**, *42*, 4645–4648.
32 R. Chinchilla, P. Mazon, C. Najera, *Tetrahedron: Asymmetry* **2002**, *13*, 927–931.
33 T. Ooi, M. Kameda, K. Maruoka,

J. Am. Chem. Soc. **1999**, *121*, 6519–6520.
34 T. Ooi, M. Kameda, K. Maruoka, *J. Am. Chem. Soc.* **2003**, *125*, 5139–5151.
35 T. Ooi, E. Tayama, K. Doda, M. Takeuchi, K. Maruoka, *Synlett* **2000**, 1500–1502.
36 T. Ooi, Y. Uematsu, M. Kameda, K. Maruoka, *Angew. Chem.* **2002**, *114*, 1621–1624; *Angew. Chem. Int. Ed.* **2002**, *41*, 1551–1554.
37 T. Ooi, Y. Kubota, K. Maruoka, *Synlett* **2003**, 1931–1933.
38 T. Shibuguchi, Y. Fukuta, Y. Akachi, A. Sekine, T. Oshima, M. Shibasaki, *Tetrahedron Lett.* **2002**, *43*, 9539–9543.
39 T. Oshima, V. Gnanadesikan, T. Shibuguchi, Y. Fukuta, T. Nemoto, M. Shibasaki, *J. Am. Chem. Soc.* **2003**, *125*, 11206–11207.
40 The Shibasaki group developed a broad range of asymmetric catalytic syntheses using bifunctional catalysts. For excellent reviews, see: (a) M. Shibasaki in: *Stimulating Concepts in Chemistry* (Eds.: F. Vögtle, J. F. Stoddart, M. Shibasaki), John Wiley and Sons, New York, **2000**, p. 105–136; (b) M. Shibasaki, N. Yoshikawa, *Chem. Rev.* **2002**, *102*, 2187–2210.
41 T. Kita, A. Georgieva, Y. Hashimoto, T. Nakata, K. Nagasawa, *Angew. Chem.* **2002**, *114*, 2956–2958; *Angew. Chem. Int. Ed.* **2002**, *41*, 2832–2834.
42 K. Nagasawa, A. Georgieva, H. Takahashi, T. Nakata, *Tetrahedron* **2001**, *57*, 8959–8964.
43 B. Imperiali, S. L. Fisher, *J. Org. Chem.* **1992**, *57*, 757–759.
44 K. J. Kise, Jr., B. E. Bowler, *Tetrahedron: Asymmetry* **1998**, *9*, 3319–3324.
45 A. Torrado, B. Imperiali, *J. Org. Chem.* **1996**, *61*, 8940–8948.
46 B. Imperiali, R. S. Roy, *J. Org. Chem.* **1995**, *60*, 1891–1894.
47 A. V. R. Rao, K. L. Reddy, A. S. Rao, T. V. S. K. Vittal, M. M. Reddy, P. L. Pathi, *Tetrahedron Lett.* **1996**, *37*, 3023–3026.
48 E. J. Corey, M. C. Noe, F. Xu, *Tetrahedron Lett.* **1998**, *39*, 5347–5350.
49 M. C. Pirrung, N. Krishnamurthy, *J. Org. Chem.* **1993**, *58*, 954–956.
50 T. Ooi, M. Kameda, H. Tannai, K. Maruoka, *Tetrahedron Lett.* **2000**, *41*, 8339–8342.
51 T. Ooi, Y. Uematsu, M. Kameda, K. Maruoka, *Synthesis* **2001**, 1716–1718.
52 T. Ooi, E. Tayama, K. Maruoka, *Angew. Chem.* **2003**, *115*, 559–602; *Angew. Chem. Int. Ed.* **2003**, *42*, 579–582.
53 For selected examples, see. (a) T. Wirth, *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 225–227; (b) C. Cativiela, M. D. Diaz-de-Villegas, *Tetrahedron: Asymmetry* **1998**, *9*, 3517–3599; (c) U. Koert, *Nachr. Chem. Tech.* **1995**, *43*, 347.
54 Y. Ito, M. Sawamura, E. Shirakawa, K. Hayashizaki, T. Hayashi, *Tetrahedron* **1988**, *44*, 5253–5262.
55 Y. Ito, M. Sawamura, M. Matsuoka, Y. Matsumoto, T. Hayashi, *Tetrahedron Lett.* **1987**, *28*, 4849–4852.
56 M. J. O'Donnell, S. Wu, *Tetrahedron: Asymmetry* **1992**, *3*, 591–594.
57 B. Lygo, J. Crosby, J. A. Peterson, *Tetrahedron Lett.* **1999**, *40*, 8671–8674.
58 T. Ooi, M. Takeuchi, M. Kameda, K. Maruoka, *J. Am. Chem. Soc.* **2000**, *122*, 5228–5229.
59 Y. N. Belokon, K. A. Kochetkov, T. D. Churkina, N. S. Ikonnikov, A. A. Chesnokov, O. V. Larionov, I. Singh, V. S. Parmar, S. Vyskocil, H. B. Kagan, *J. Org. Chem.* **2000**, *65*, 7041–7048.
60 Y. N. Belokon, K. A. Kochetkov, T. D. Churkina, N. S. Ikonnikov, A. A. Chesnokov, O. V. Larionov, V. S. Parmar, R. Kumar, H. B. Kagan, *Tetrahedron: Asymmetry* **1998**, *9*, 851–857.
61 Y. N. Belokon, K. A. Kochetkov, T. D. Churkina, N. S. Ikonnikov, S. Vyskocil, H. B. Kagan, *Tetrahedron: Asymmetry* **1999**, *10*, 1723–1728.
62 B. Lygo, J. Crosby, J. A. Peterson, *Tetrahedron Lett.* **1999**, *40*, 1385–1388.
63 B. Lygo, *Tetrahedron Lett.* **1999**, *40*, 1389–1392.
64 M. J. O'Donnell, F. Delgado,

C. Hostettler, R. Schwesinger, *Tetrahedron Lett.* **1998**, *39*, 8775–8778.

65 M. J. O'Donnell, F. Delgado, R. S. Pottorf, *Tetrahedron* **1999**, *55*, 6347–6362.

66 R. Chinchilla, P. Mazon, C. Najera, *Tetrahedron: Asymmetry* **2000**, *11*, 3277–3281.

67 (a) B. Thierry, T. Perrard, C. Audouard, J.-C. Plaquevent, D. Cahard, *Synthesis* **2001**, 1742–1746; (b) B. Thierry, J.-C. Plaquevent, D. Cahard, *Tetrahedron: Asymmetry* **2001**, *12*, 983–986.

68 (a) B. Thierry, J.-C. Plaquevent, D. Cahard, *Tetrahedron: Asymmetry* **2003**, *14*, 1671–1677; (b) T. Danelli, R. Annunziata, M. Benaglia, M. Cinquini, F. Cozzi, G. Tocco, *Tetrahedron: Asymmetry* **2003**, *14*, 461–467; (c) T. Okino, Y. Takemoto, *Org. Lett.* **2001**, *3*, 1515–1517.

69 E. J. Corey, Y. Bo, J. Busch-Petersen, *J. Am. Chem. Soc.* **1998**, *120*, 13000–13001.

70 N. Vignola, B. List, *J. Am. Chem. Soc.* **2004**, *126*, 450–451.

71 J. March, *Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, 4th ed. John Wiley and Sons, New York, **1992**.

72 F. A. Davis, H. Qi in: *Enantio-controlled Synthesis of Fluoro-Organic Compounds*, V. A. Soloshonok (Ed.), John Wiley and Sons, Chichester, **1999**, pp. 1–32.

73 F. A. Davis, P. V. N. Kasu, *Org. Prep. Proced. Int.* **1999**, *31*, 125–143.

74 E. Differding, R. W. Lang, *Tetrahedron Lett.* **1988**, *29*, 6087–6090.

75 F. A. Davis, P. Zhou, C. K. Murphy, G. Sundarababu, H. Qi, R. M. Przeslawski, B.-C. Chen, P. J. Carroll, *J. Org. Chem.* **1998**, *63*, 2273–2280, and references cited therein.

76 Y. Takeuchi, T. Suzuki, A. Satoh, T. Shiragami, N. Shibata, *J. Org. Chem.* **1999**, *64*, 5708–5711.

77 Y. Takeuchi, A. Satoh, T. Suzuki, A. Kameda, M. Dohrin, T. Satoh, T. Koizumi, K. L. Kirk, *Chem. Pharm. Bull.* **1997**, *45*, 1085–1088.

78 N. Shibata, E. Suzuki, Y. Takeuchi, *J. Am. Chem. Soc.* **2000**, *122*, 10728–10729.

79 N. Shibata, E. Suzuki, T. Asahi, M. Shiro, *J. Am. Chem. Soc.* **2001**, *123*, 7001–7009.

80 D. Cahard, C. Audouard, J.-C. Plaquevent, N. Roques, *Org. Lett.* **2000**, *2*, 3699–3701.

81 D. Cahard, C. Audouard, J.-C. Plaquevent, L. Toupet, N. Roques, *Tetrahedron Lett.* **2001**, *42*, 1867–1869.

82 B. Mohar, J. Baudoux, J.-C. Plaquevent, D. Cahard, *Angew. Chem.* **2001**, *113*, 4339–4341; *Angew. Chem. Int. Ed.* **2001**, *40*, 4214–4216.

83 (a) H. Wack, A. E. Taggi, A. M. Hafez, W. J. Drury, III, T. Lectka, *J. Am. Chem. Soc.* **2001**, *123*, 1531–1532; (b) S. France, H. Wack, A. E. Taggi, A. M. Hafez, T. R. Wagerle, M. M. Shah, C. L. Dusich, T. Lectka, *J. Am. Chem. Soc.* **2004**, *126*, 4245–4255.

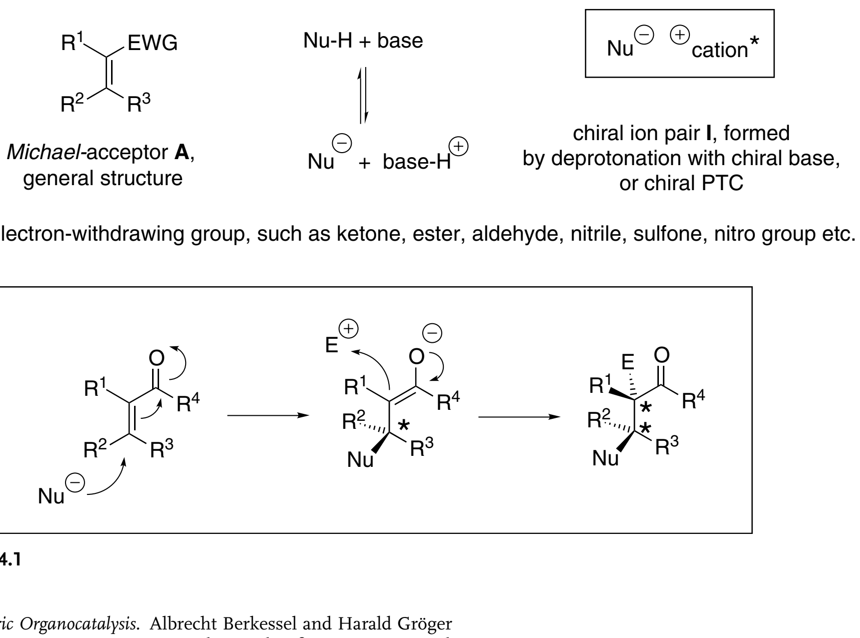
84 M. P. Brochu, S. P. Brown, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2004**, *126*, 4108–4109.

85 N. Halland, A. Braunton, S. Bachmann, M. Marigo, K. A. Jørgensen, *J. Am. Chem. Soc.* **2004**, *126*, 4790–4791.

4
Nucleophilic Addition to Electron-deficient C=C Double Bonds

4.1
Intermolecular Michael Addition

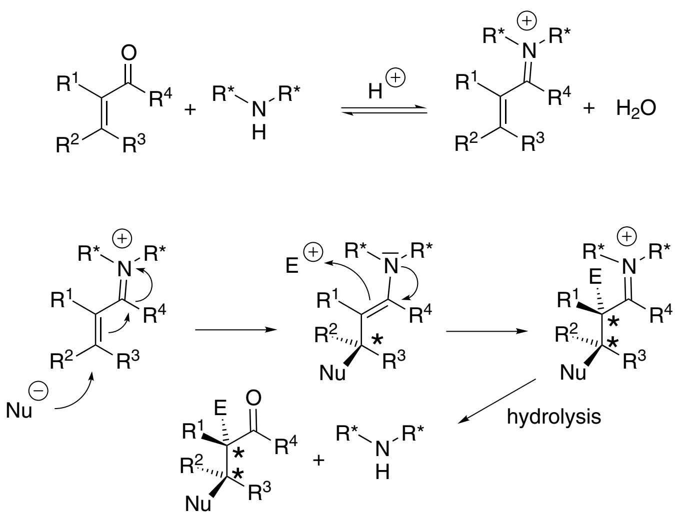
In the Michael-addition, a nucleophile Nu^- is added to the β-position of an α,β-unsaturated acceptor A (Scheme 4.1) [1]. The active nucleophile Nu^- is usually generated by deprotonation of the precursor NuH. Addition of Nu^- to a prochiral acceptor A generates a center of chirality at the β-carbon atom of the acceptor A. Furthermore, the reaction of the intermediate enolate anion with the electrophile E^+ may generate a second center of chirality at the α-carbon atom of the acceptor. This mechanistic scheme implies that enantioface-differentiation in the addition to the β-carbon atom of the acceptor can be achieved in two ways: (i) deprotonation of NuH with a chiral base results in the chiral ion pair I which can be expected to add to the acceptor asymmetrically; and (ii) phase-transfer catalysis (PTC) in which deprotonation of NuH is achieved in one phase with an achiral base and the anion



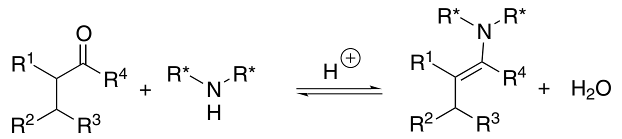
Scheme 4.1

Asymmetric Organocatalysis. Albrecht Berkessel and Harald Gröger
Copyright © 2005 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim
ISBN: 3-527-30517-3

(a) Activation of the *Michael*-acceptor by iminium ion formation



(b) Activation of a carbonyl donor by enamine formation



Scheme 4.2

Nu^- is transported into the organic phase by a chiral phase-transfer catalyst, again resulting in a chiral ion pair from which asymmetric β-addition may proceed.

This method of providing a chiral environment for the attacking nucleophile can be regarded as the "classical" way of approaching asymmetric organocatalysis of Michael additions and will be discussed for C-nucleophiles in Section 4.1.1.1. In recent years, two highly efficient and very practical alternatives have emerged (Scheme 4.2). One of these approaches consists in activating the acceptors – mostly α,β-unsaturated aldehydes ($R^4 = H$) and ketones ($R^4 =$ alkyl) – by reversible conversion to a chiral iminium ion. As shown in Scheme 4.2a, reversible condensation of an α,β-unsaturated carbonyl compound with a chiral secondary amine provides a chiral α,β-unsaturated iminium ion. Face-selective reaction with the nucleophile provides an enamine which can either be reacted with an electrophile then hydrolyzed or just hydrolyzed to a β-chiral carbonyl compound. The second approach is the enamine pathway. If the nucleophile is an enolate anion, it can be replaced by a chiral enamine, formed reversibly from the original carbonyl compound and a chi-

ral secondary amine (Scheme 4.2b). Both the iminium ion and enamine methods will be discussed for C-nucleophiles in Section 4.1.1.2. Section 4.1.1.3 summarizes recent results of organocatalyzed Michael additions to azodicarboxylates, which provide facile access to α-aminated carbonyl compounds such as α-amino acids. This reaction type is also reviewed in chapter 7, together with nucleophilic additions to the N=O double bond. Finally, Section 4.1.1.4 reports a recent example of an organocatalytic cyclopropanation of enoates with phenacyl halides.

Section 4.1.2 covers N- and O-nucleophiles and Section 4.1.3 covers S- and Se-nucleophiles.

4.1.1
Intermolecular Michael Addition of C-nucleophiles

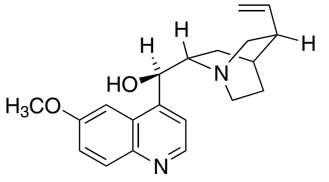
4.1.1.1 Chiral Bases and Phase-transfer Catalysis

The first examples of asymmetric Michael additions of C-nucleophiles to enones appeared in the middle to late 1970s. In 1975 Wynberg and Helder demonstrated in a preliminary publication that the quinine-catalyzed addition of several acidic, doubly activated Michael donors to methyl vinyl ketone (MVK) proceeds asymmetrically [2, 3]. Enantiomeric excesses were determined for addition of α-tosylnitroethane to MVK (56%) and for 2-carbomethoxyindanone as the pre-nucleophile (68%). Later Hermann and Wynberg reported in more detail that 2-carbomethoxyindanone (**1**, Scheme 4.3) can be added to methyl vinyl ketone with ca 1 mol% quinine (**3a**) or quinidine (**3b**) as catalyst to afford the Michael-adduct **2** in excellent yields and with up to 76% ee [2, 4]. Because of their relatively low basicity, the amine bases **3a**,**b** do not effect the Michael addition of less acidic pre-nucleophiles such as **4** (Scheme 4.3). However, the corresponding ammonium hydroxides **6a**,**b** do promote the addition of the substrates **4** to methyl vinyl ketone under the same mild conditions, albeit with enantioselectivity not exceeding ca 20% [4].

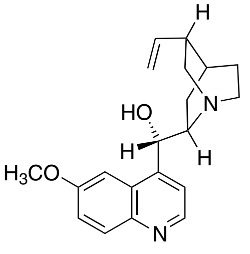
Michael additions of C-nucleophiles such as the indanone **1** have been the subject of numerous further studies: For example, the reaction between the indanone **1** and methyl vinyl ketone was effected by a solid-phase-bound quinine derivative in 85% yield and with remarkable 87% ee by d'Angelo, Cavé et al. [5]. Co-polymers of cinchona alkaloids with acrylonitrile effected the same transformation; Kobayashi and Iwai [6a] achieved 92% yield and 42% ee and Oda et al. [6b] achieved almost quantitative yield and up to 65% ee. Similarly, partially resolved 2-(hydroxymethyl)quinuclidine was found to catalyze the reaction between **1** and acrolein and α-isopropyl acrolein with induction of asymmetry, but no enantiomeric excesses were determined [7]. As shown in Scheme 4.4, the indanone **7** could be added to MVK with up to 80% ee under phase-transfer conditions, by use of the Cinchona-derived PT-catalysts **9a** and **9b**, affording the Michael-product **8** or *ent*-**8**, respectively [8]. The adducts **8** or *ent*-**8** were intermediates in the stereoselective Robinson anellation of a cyclohexenone ring to the indanone **7** [8].

The best selectivity in the Michael addition of 2-carboxycyclopentanones to an enone or enal were recently achieved by Maruoka et al. [9]. As shown in Scheme 4.5, as little as 2 mol% of the binaphthyl-derived phase-transfer catalyst **10** – in the presence of 10 mol% solid potassium carbonate – enabled the highly efficient

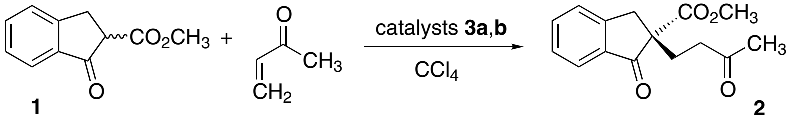
chiral base catalysts:



quinine **3a**



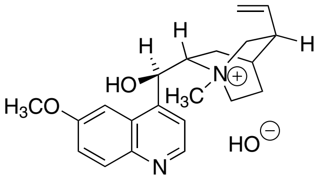
quinidine **3b**



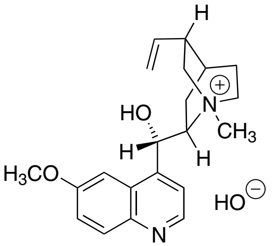
1 **2**

Catalyst (% loading)	Temp. (°C)	Yield (%)	ee (%)	Configuration of major product
3a (1 mol-%)	- 21	99	76	*S*
3a (1 mol-%)	+ 25	98	60	*S*
3b (1 mol-%)	- 21	quant.	69	*R*

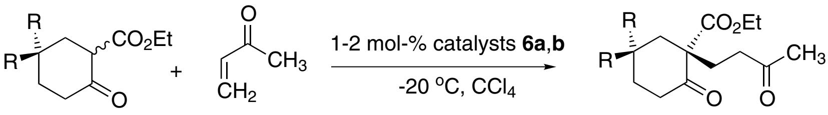
chiral base catalysts:



quinine-derived catalyst **6a**



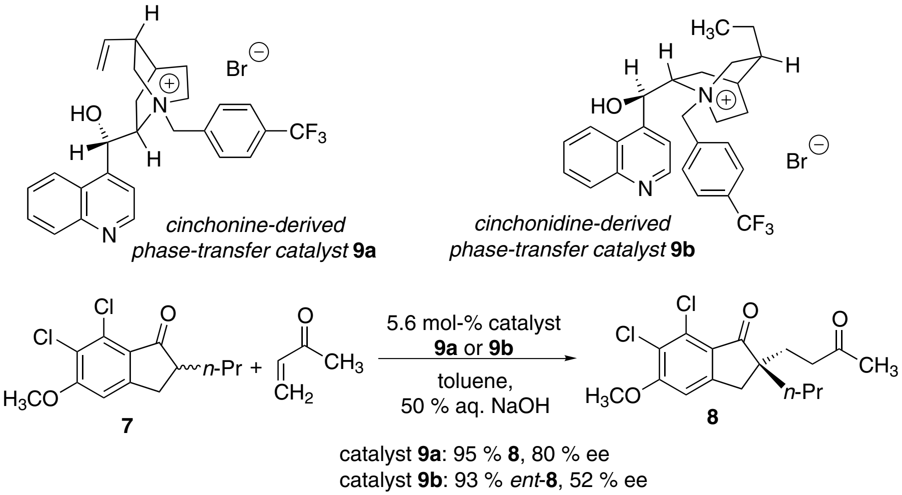
quinidine-derived catalyst **6b**



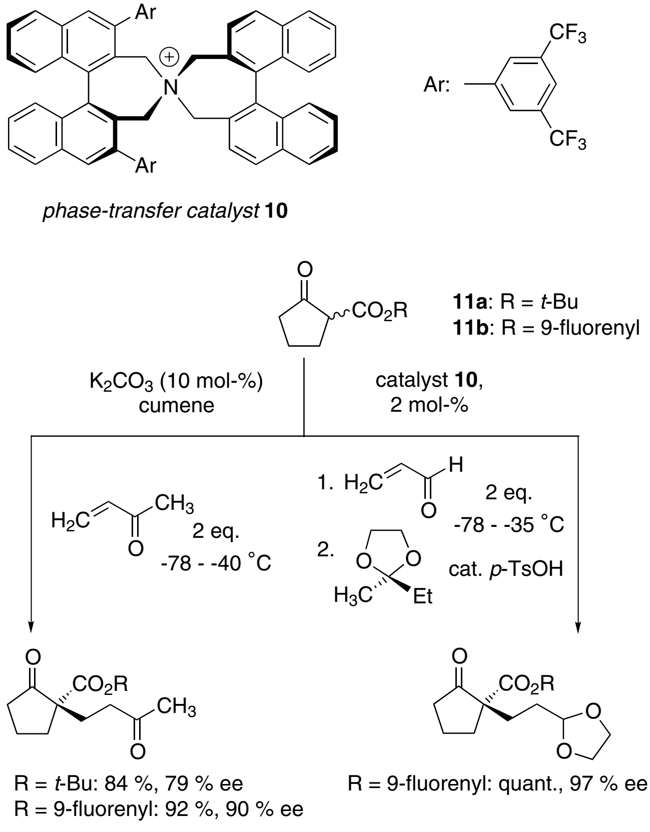
4
R = H, -O-CH$_2$-CH$_2$-O-, -S-CH$_2$-CH$_2$-S-

5
catalyst **6a**: up to 99 %, 22 % ee (*R*) at -20 °C
catalyst **6b**: 99 %, 9 % ee (*S*) at +25 °C

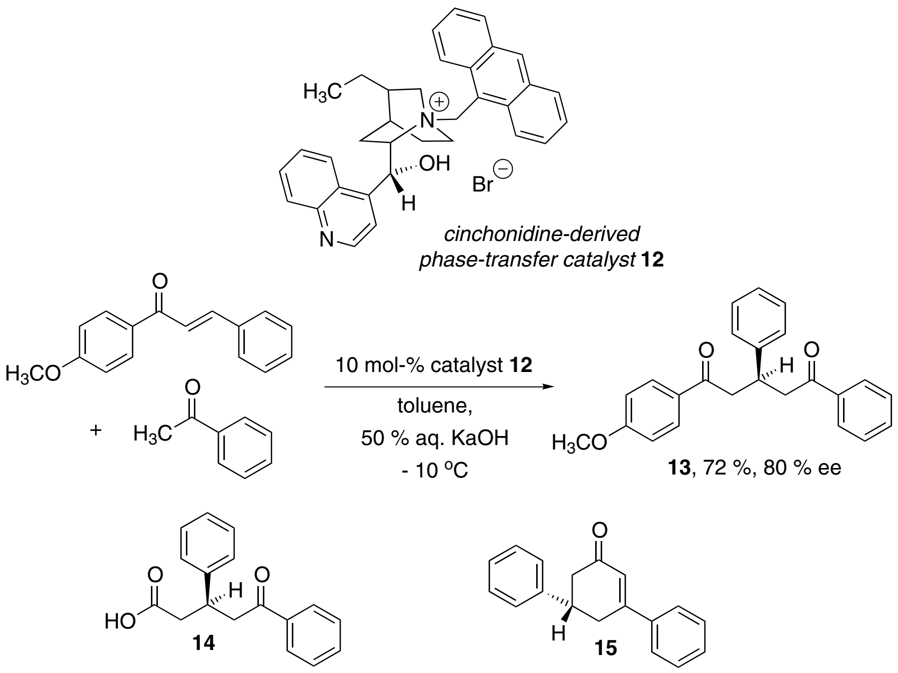
Scheme 4.3



Scheme 4.4



Scheme 4.5



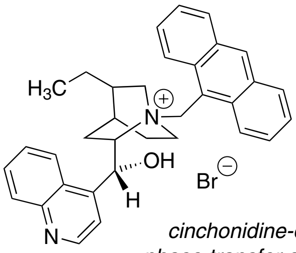
Scheme 4.6

and enantioselective (up to 97% ee) addition of the 2-carboxycyclopentanones *rac*-**11a**,**b** to methyl vinyl ketone and acrolein [9].

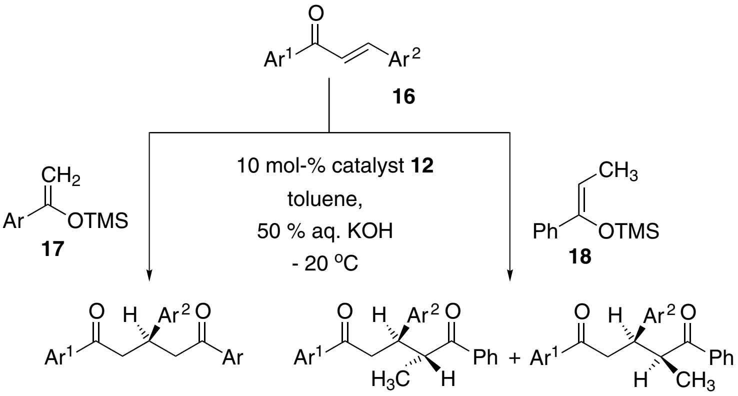
Aqueous-organic biphasic PTC-conditions were used by Zhang and Corey for addition of acetophenone to 4-methoxychalcone in the presence of the *N*-(9-anthracenylmethyl)dihydrocinchonidinium salt **12**, affording the *S*-configured adduct **13** in 72% yield and 80% ee (Scheme 4.6) [10].

The utility of this process was further illustrated by the conversion of **13** to the δ-keto acid **14** or the 2-cyclohexenone **15**. The same authors later showed that the phase-transfer catalyst **12** also enables the highly enantioselective addition of the silyl enol ethers **17** to the chalcones **16** (Scheme 4.7) [11].

Use of the preformed *Z*-silyl enol ether **18** results in quite substantial anti/syn selectivity (**19**:**20**; up to 20:1), with enantiomeric purity of the anti adducts reaching 99%. The chiral PT-catalyst **12** (Schemes 4.6 and 4.7) proved just as efficient in the conjugate addition of the *N*-benzhydrylidene glycine *tert*-butyl ester (**22**, Scheme 4.8) to acrylonitrile, affording the Michael adduct **23** in 85% yield and 91% ee [10]. This primary product was converted in three steps to L-ornithine [10]. The *O*-allylated cinchonidine derivative **21** was used in the conjugate addition of **22** to methyl acrylate, ethyl vinyl ketone, and cyclohexenone (Scheme 4.8) [12]. The Michael-adducts **24**–**26** were obtained with high enantiomeric excess and, for cyclohexenone as acceptor, with a remarkable (25:1) ratio of diastereomers (**26**, Scheme 4.8). In the last examples solid (base)–liquid (reactants) phase-transfer was applied.



cinchonidine-derived phase-transfer catalyst **12**



18, 79-92 %, 91-95 % ee

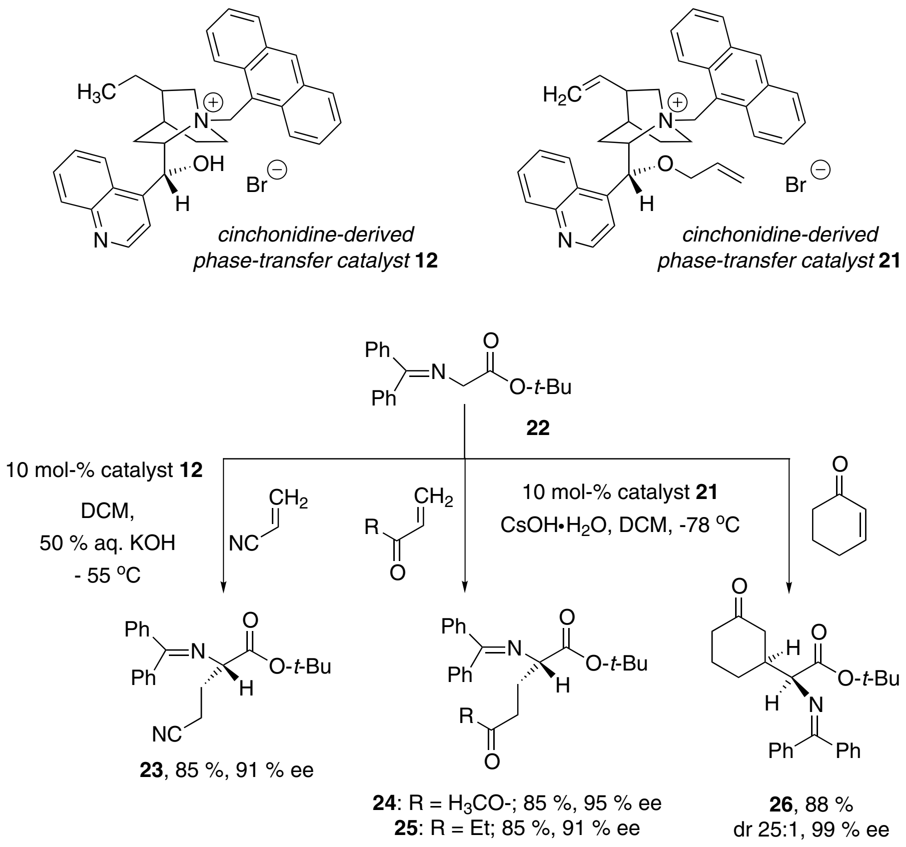
19, *anti* (2*R*, 3*R*)

20, *syn* (2*S*, 3*R*)

Addition of the silyl enol ether **18** to the enones **16**:

R^1	R^2	**19:20** *anti/syn*	**19** (*anti*) yield (ee) [%]	**20** (*syn*) yield (ee) [%]
C_6H_5-	C_6H_5-	9:1	81 (99)	9 (90)
4-F-C_6H_4-	C_6H_5-	10:1	86 (99)	9 (94)
4-Br-C_6H_4-	C_6H_5-	10:1	80 (99)	8 (84)
4-CH_3O-C_6H_4-	C_6H_5-	4:1	75 (98)	18 (90)
C_6H_5-	4-CH_3-C_6H_4-	10:1	78 (99)	7 (81)
C_6H_5-	4-NO_2-C_6H_4-	3:1	65 (97)	22 (95)
C_6H_5-	4-Br-C_6H_4-	7:1	82 (92)	12 (95)
C_6H_5-	1-$C_{10}H_7$-	20:1	82 (92)	- - -

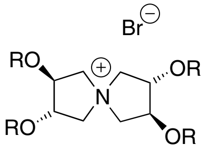
Scheme 4.7



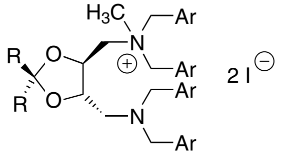
Scheme 4.8

The asymmetric addition of glycine enolates to acrylates was also achieved by use of the tartaric acid-derived phase-transfer catalysts **27** and **28** (Scheme 4.9). Arai, Nishida and Tsuji [13] showed that the C_2-symmetric ammonium cations **27a**,**b** afford up to 77% ee when *t*-butyl acrylate is used as acceptor. The cations **28** are the most effective/selective PTC identified by broad variation of the substituents present on both the acetal moiety and nitrogen atoms [14]. In this study by Shibasaki et al. enantiomeric excesses up to 82% were achieved by use of the catalyst **28a** (Scheme 4.9) [14]. Scheme 4.9 also shows the structure of the guanidine **29** prepared by Ma and Cheng; in the absence of additional base this also catalyzes the Michael addition of the glycine derivative **22** to ethyl acrylate, albeit with modest ee of 30% [15].

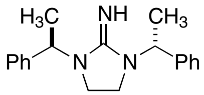
By a similar but solvent-free method Plaquevent et al. produced the Michael adduct **30** from 2-pentyl-2-cyclopentenone in 91% yield and with 90% ee, by use of the quinine-derived catalyst **31** (Scheme 4.10) [16]. When the quinidine-derived ammonium salt **32** was employed, 80% of the enantiomeric product *ent*-**30** was ob-



27a: R = Bn
27b: R = 4-CF_3-Bn



28a: R = *n*-Pr, Ar = 4-Me-C_6H_4
28b: R = *n*-Bu, Ar = 4-Me-C_6H_4

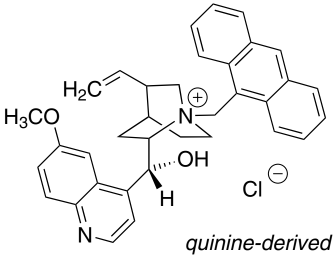


29

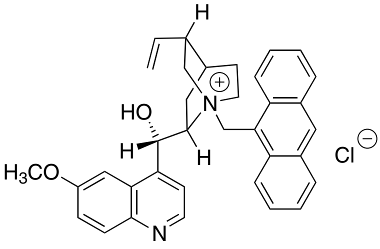
Additions of N-benzhydrylidene glycine *tert.*-butyl ester (**22**, see Scheme 4.8) to alkyl acrylates:

Acrylate	Base	Solvent (temp.)	Catalyst	Catalyst loading (mol-%)	Yield [%]	ee [%]	Ref.
t-Butyl	CsOH•H_2O	*t*-BuOMe (-60 °C)	**27a**	10	86	73	13
t-Butyl	CsOH•H_2O	*t*-BuOMe (-60 °C)	**27b**	10	73	77	13
Methyl	Cs_2CO_3	C_6H_5Cl (4 °C)	**28a**	10	94	64	14
Methyl	Cs_2CO_3	C_6H_5Cl (4 °C)	**28b**	10	89	64	14
Methyl	Cs_2CO_3	C_6H_5Cl (-30 °C)	**28a**	10	86	75	14
Ethyl	Cs_2CO_3	C_6H_5Cl (-30 °C)	**28a**	10	88	82	14
n-Butyl	Cs_2CO_3	C_6H_5Cl (-30 °C)	**28a**	10	79	78	14
Ethyl	none	THF (-78 - -10 °C)	**29**	20	99	30	15

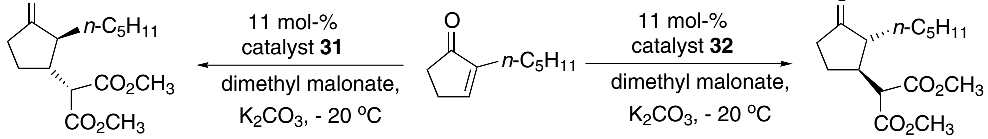
Scheme 4.9



quinine-derived phase-transfer catalyst **31**



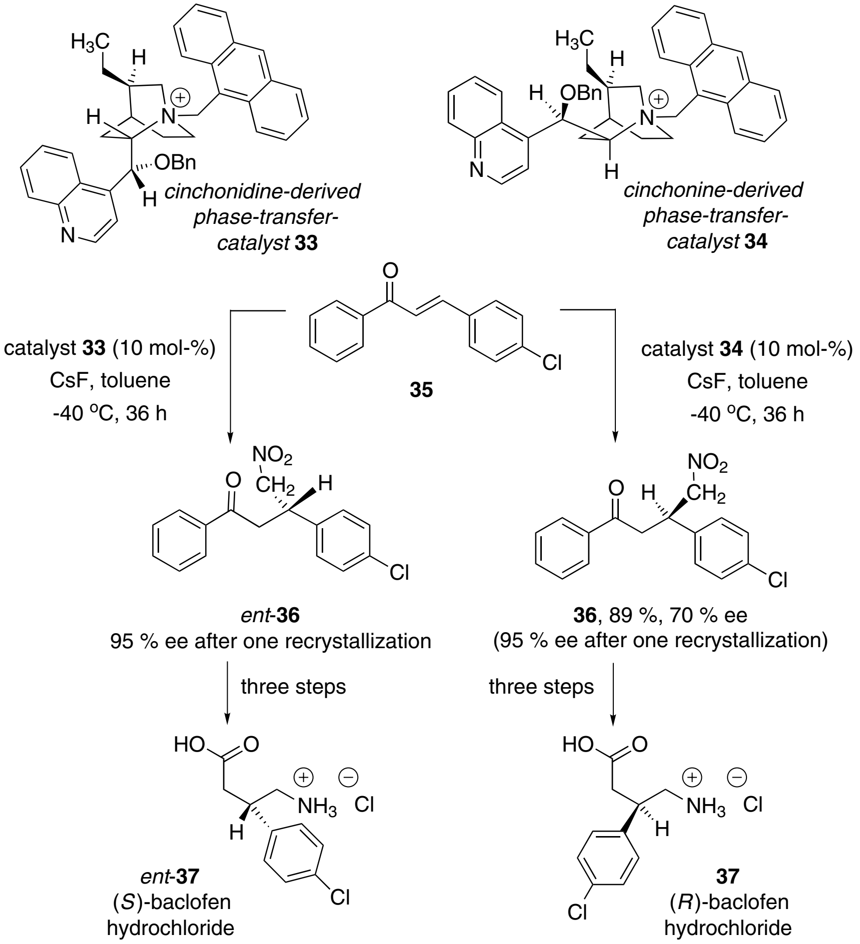
quinidine-derived phase-transfer catalyst **32**



30, 90 %, 91 % ee

ent-**30**, 80 %, 60 % ee

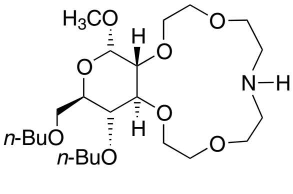
Scheme 4.10



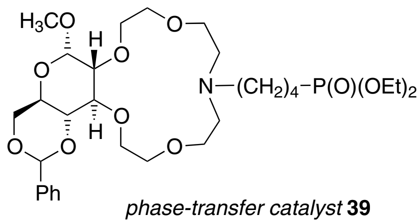
Scheme 4.11

tained, in 60% ee (Scheme 4.10). The Michael adducts **30** and *ent*-**30** served as intermediates in the synthesis of (+)- and (−)-dihydrojasmonate, respectively [16].

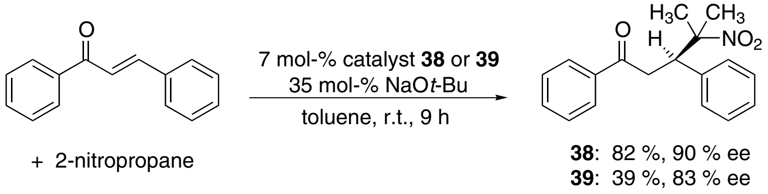
Nitroalkanes are another important class of pre-nucleophiles. Again, Wynberg and co-workers were among the first (1975) to report the enantioselective Michael addition of nitroalkanes, albeit without quantitative determination of the ratio of product enantiomers [2]. As for ketone and ester C-nucleophiles, chiral amine bases can be employed only if the pre-nucleophile is sufficiently acidic, i.e. usually doubly activated by two electron-withdrawing functional groups. In 1978 Colonna, Hiemstra, and Wynberg reported that addition of nitromethane to chalcone can be effected by the more basic *N*-benzylquininium or *N*-dodecylephedrinium fluorides, and enantioselectivity of up to 23% ee was observed [17]. Significantly improved enantioselectivity was reported by Corey and Zhang when the *N*-(9-anthracenylmethyl)cinchonine derivative **34** (Scheme 4.11) was used as phase-transfer catalyst



phase-transfer catalyst **38**



phase-transfer catalyst **39**



Scheme 4.12

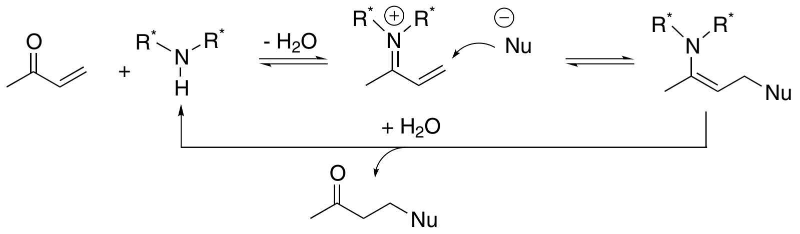
in the addition of nitromethane to the chalcone **35**. In the presence of solid CsF as base the Michael-adduct **36** was obtained in 89% yield and 70% ee. The enantiomeric purity of the latter was enhanced to 95% ee by one recrystallization. The nitro compound **36** served as a precursor in the synthesis of the enantiomerically pure pharmaceutical compound (*R*)-baclofen (**37**, Scheme 4.11) [18]. Analogously, (*S*)-baclofen (*ent*-**37**) was obtained *via* the nitro intermediate *ent*-**36** by using the cinchonidine-derived phase-transfer catalyst **33** (Scheme 4.11) [18].

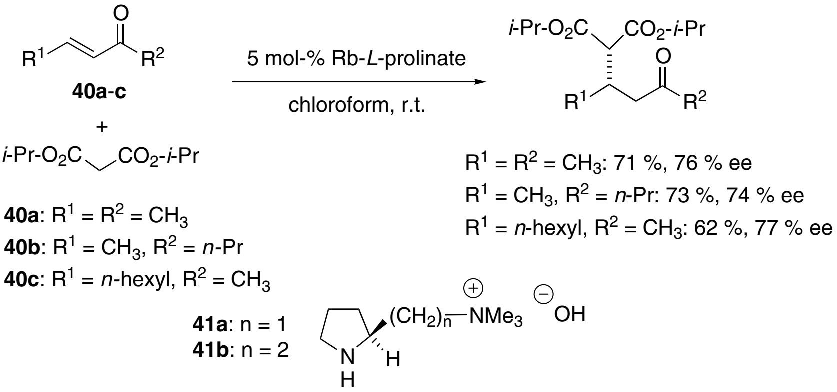
In the addition of 2-nitropropane to chalcone Töke et al. achieved 90% ee by using the D-glucose-derived chiral crown ether **38** as phase-transfer catalyst (Scheme 4.12) [19]. The related crown ether **39**, with a pendant phosphonate group, afforded the chalcone adduct with 83% ee, albeit with only 39% chemical yield (Scheme 4.12) [20]. *N*-Alkylated or *N*-arylated derivatives of the crown ether **38** afforded lower ee (max. 60%) in the addition of 2-nitropropane to chalcone [21].

4.1.1.2 **Activation of Michael Acceptors by Iminium Ion Formation, Activation of Carbonyl Donors by Enamine Formation**

Cheap and readily available L-proline has been used numerous times for the intermediate and reversible generation of chiral iminium ions from α,β-unsaturated carbonyl compounds. For example, Yamaguchi et al. reported in 1993 that the rubidium salt of L-proline catalyzes the addition of di-*iso*-propyl malonate to the acyclic Michael acceptors **40a–c** (Scheme 4.13), with enantiomeric excesses as high as 77% [22]. With 2-cycloheptenone and 2-cyclohexenone as substrates ca 90% yield and ee of 59% and 49% were obtained. Later the enantioselectivity of this process was increased to a maximum of 88% ee in the addition of di-*tert*-butyl malonate to the *E*-pentenone **40a** in the presence of 20 mol% Rb-L-prolinate and 20 mol% CsF [23]. Taguchi and Kawara employed the L-proline-derived ammonium salts **41a** and

Catalysis by iminium ion formation



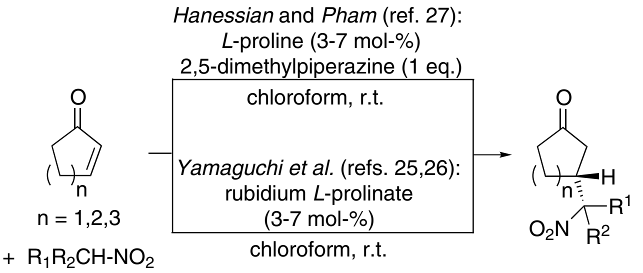


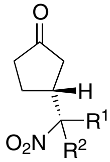
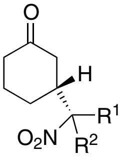
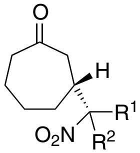
Scheme 4.13

41b as catalysts (Scheme 4.13) [24]. In the presence of 10 mol% **41a** addition of dibenzyl malonate to cyclohexenone proceeded with 71% ee (61% yield). Similar ee were observed with dimethyl malonate as nucleophile or with cyclopentenone or benzylidene acetone as acceptors [24].

Yamaguchi et al. also showed that Rb-L-prolinate catalyzes enantioselective addition of nitroalkanes to several acyclic and cyclic enones [25, 26]. For acyclic enone acceptors the best result, i.e. 74% yield and 68% ee of the *S* product, was achieved in the addition of 2-nitropropane to *E*-3-penten-2-one (**40a**, Scheme 4.13) [25]. Screening of several proline derivatives and cyclic amino acids of other ring size resulted in the identification of the *O*-TBDMS-derivative of 4-hydroxyproline as the best catalyst for addition of nitrocyclohexane to cycloheptenone. In this particular reaction 74% yield and 86% ee were achieved [26].

The proline-catalyzed conjugate addition of nitroalkanes was further developed by Hanessian and Pham, resulting in enantiomeric excesses up to 93% in the addition of a variety of nitroalkanes to cyclic enones (Scheme 4.14) [27]. In their catalytic system, L-proline (3–7 mol%) was employed together with equimolar amounts (relative to the substrate enones) of *trans*-2,5-dimethylpiperazine. The latter addi-

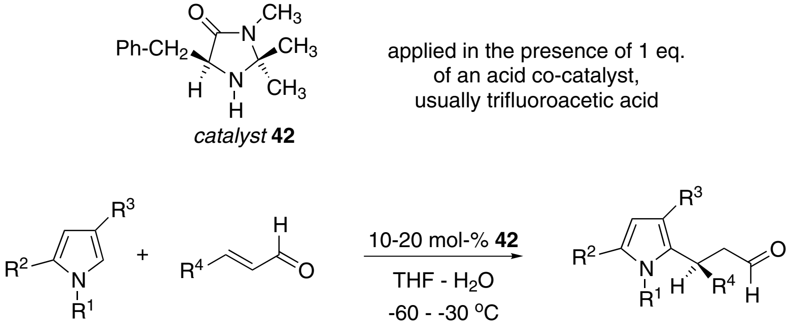


Michael-products:	R^1, R^2	Yield [%]	ee [%][a]	ee [%][b]
	-H	30	62	- - -
	$-CH_3$	66	75	12
	$-(CH_2)_4-$	66	76	37
	$-(CH_2)_5-$	62	76	- - -
	-H	61	71	45
	$-CH_3$	88	93	59
	$-(CH_2)_4-$	68	93	75
	$-(CH_2)_5-$	73	93	80
	$-CH_3$	61	86	73
	$-(CH_2)_4-$	71	87	67
	$-(CH_2)_5-$	49	89	86

[a] ee achieved by *Hanessian* and *Pham* with the *L*-proline - *trans*-2,5-dimethylpiperazine catalyst (ref. 27).
[b] ee achieved by *Yamaguchi et al.* using rubidium prolinate as catalyst (refs. 25,26).

Scheme 4.14

tive was identified by broad screening of basic additives, as was dry chloroform as solvent. From the pronounced nonlinear effect observed, the authors concluded that "a complex multicomponent chiral catalytic system is operative" [27]. Enantioselectivity achieved with Rb-L-prolinate and with L-proline + *trans*-2,5-dimethylpiperazine is compared in Scheme 4.14. In both the Yamaguchi and Hanessian systems primary nitroalkanes such as nitroethane could also be added to enones. Usually, the diastereomeric Michael adducts were formed in ratios of 1:1 to 2:1.



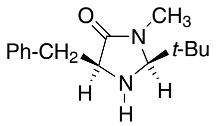
R^1	R^2	R^3	R^4	Yield (%)	ee (%)
Me	H	H	Me	83	91
Me	H	H	*n*-Pr	81	90
Me	H	H	*i*-Pr	80	91
Me	H	H	Ph	87	93
Bn	H	H	Ph	80	89
Allyl	H	H	Ph	83	91
Me	*n*-Bu	H	Ph	87	90
Me	H	*n*-Pr	Ph	68	97
Me	H	H	4-MeOPh	79	91
Me	H	H	CH_2OBn	90	87
Me	H	H	CO_2Me	72	90
H	H	H	CO_2Me	74	90

Scheme 4.15

The enantiomeric purities of these materials were found to be in the range 60–90% [25–27].

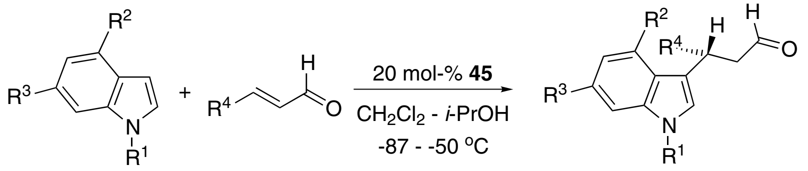
More recently, MacMillan has introduced the amine catalysts **42** and **45**, readily available from L-phenylalanine, methylamine, and acetone or pivalaldehyde, respectively (Schemes 4.15 and 4.16). The broad potential of these materials in enantioselective organocatalysis was first proven in Diels–Alder reactions [28] and nitrone cycloadditions [29]. In 1,4-addition of C-nucleophiles MacMillan et al. later showed that Friedel–Crafts reactions of pyrroles with enals can be made highly enantioselective (Scheme 4.15) [30].

For best catalytic efficiency and selectivity trifluoroacetic acid was identified as the optimum co-catalyst for most substrates [30]. Double alkylation of *N*-methylpyrrole in the presence of the catalyst **42** can be performed either with an excess of one enal electrophile, e.g. crotonaldehyde, affording the 2,5-disubstituted product **43** in 83% chemical yield, a C_2/C_s ratio of 9:1, and with 98% ee of the C_2-symmetric



catalyst **45**

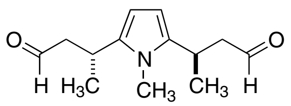
applied in the presence of 1 eq. of an acid co-catalyst, usually trifluoroacetic acid



R^1	R^2	R^3	R^4	Yield (%)	ee (%)
Me	H	H	Me	82	92
Me	H	H	*n*-Pr	80	93
Me	H	H	*i*-Pr	74	93
Me	H	H	CH_2OBn	84	96
Me	H	H	Ph	84	90
Me	H	H	CO_2Me	89	91
H	H	H	Me	72	91
Allyl	H	H	Me	70	92
CH_2Ph	H	H	Me	80	89
H	Me	H	Me	94	94
Me	OMe	H	Me	90	96
H	H	Cl	Me	73	97

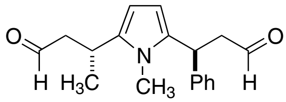
Scheme 4.16

dialkylation product. The same high selectivity is achieved when the two alkylation steps are performed successively with two *different* enal electrophiles, e.g. crotonaldehyde and cinnamaldehyde, affording the bis-alkylation product **44** [30].



43

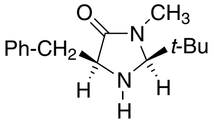
83 %, C_2 : *meso* = 9:1, 98 % ee



44

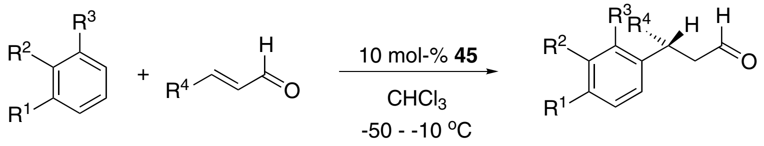
72 %, *anti* : *syn* = 9:1, 99 % ee (*anti*)

On the basis of molecular modeling studies, MacMillan et al. optimized their original amine catalyst **42** to the mono-*tert*-butylated structure **45** [31]. As summarized in Scheme 4.16, this catalyst enables highly enantioselective 1,4-addition of



catalyst **45**

applied in the presence of 1 eq. of hydrochloric acid as co-catalyst



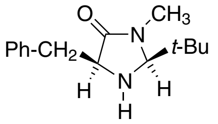
R^1	R^2	R^3	R^4	Yield (%)	ee (%)
1-Pyrrolidino	H	H	Me	70	87
NMe_2	H	H	Et	68	88
NMe_2	H	H	CH_2OBn	89	92
NMe_2	H	H	CO_2Me	90	96
1-Pyrrolidino	H	H	Ph	82	84
1-Pyrrolidino	H	H	*p*-Cl-Ph	80	92
NMe_2	H	Me	CO_2Me	89	84
NMe_2	H	OMe	CO_2Me	73	91
NMe_2	H	SMe	CO_2Me	92	91
NMe_2	H	Cl	CO_2Me	73	93
1-Pyrrolidino	H	H	CO_2Me	97	97
1-Pyrrolidino	Ph	H	H	94	99
NMe_2	H	H	CO_2Me	90	96

Scheme 4.17

indoles to enals. As mentioned in Ref. [30], *β*-chiral *β*-indole butyric acids are of pharmaceutical interest as cyclooxygenase-2 inhibitors. Similarly, the catalyst **45** effects asymmetric addition of electron-rich benzene derivatives, in particular *N*,*N*-dialkylated anilines, to enals (Scheme 4.17) [31]. The authors have further broadened the scope of this reaction by introducing a methylation/reductive deamination procedure which enables the use of *N*,*N*-dialkylanilines as benzene surrogates [32].

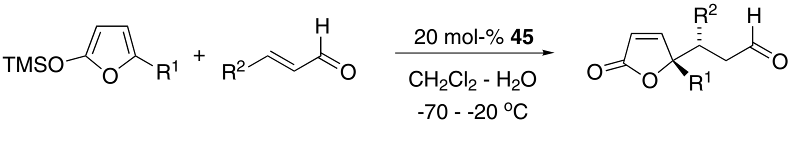
The chiral imidazolidinone **45** also catalyzes the Mukaiyama–Michael reaction between 2-silyloxy furans and *α*,*β*-unsaturated aldehydes, affording enantiomerically highly enriched *γ*-butenolides (Scheme 4.18) [33]. For optimum catalytic performance, hydroxyl additives are necessary, and addition of 2 equiv. water proved best.

Although the examples shown in Scheme 4.18 give the impression that the **45**-



catalyst **45**

applied in the presence of 1 eq.
of 2,4-dinitrobenzoic acid as co-catalyst



R^1	R^2	Yield (%)	*syn/anti*	ee (%)
Me	Me	81	22:1	92
Me	*n*-Pr	87	31:1	84
Me	*i*-Pr	80	7:1	98
Me	Ph	77	1:6	99
Me	CH_2OBn	86	20:1	90
Me	CO_2Me	84	11:1	99
H	Me	87	8:1	90
Me [a)]	Me	80	22:1	92
Et	Me	83	16:1	90

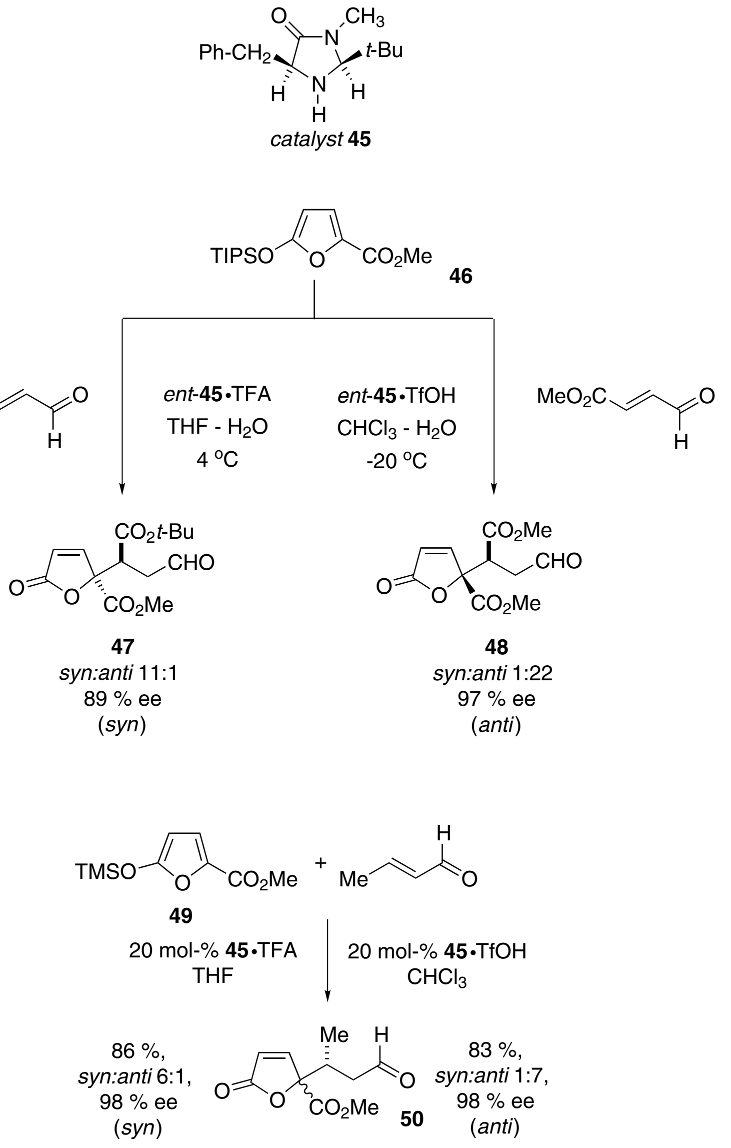
[a)] 2-TMSO-3,5-trimethylfuran affords the analogous adduct in 73 % yield, syn/anti 24:1, 90 % ee.

Scheme 4.18

catalyzed Mukaiyama–Michael addition is usually syn-selective, a delicate balance between syn- and anti-addition seems to exist; this can be shifted deliberately by appropriate choice of solvent. Some examples are summarized in Scheme 4.19 [33]. With the silyloxyfuran **46** as nucleophile, the syn (**47**) and anti adducts (**48**) can be prepared by proper choice of the acid co-catalyst, the solvent, the temperature, and the steric demand of the ester group present in the enal (Scheme 4.19, top). In the addition of furan **49** to crotonaldehyde (Scheme 4.19, bottom), *solvent and co-catalyst alone* determine which of the syn/anti diastereomers **50** is formed preferentially. For the transformations listed in Schemes 4.16 to 4.19 sub-ambient temperatures were used; these reactions can, however, often be performed – operationally more simply – at ambient temperature without significant loss of enantioselectivity.

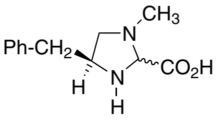
Jørgensen et al. developed the phenylalanine-derived catalyst **51** (Scheme 4.20), readily prepared in three high-yielding steps from L-phenylalanine, methylamine, and glyoxylic acid [34, 35].

In the presence of catalyst **51**, dialkyl malonates can be added asymmetrically to

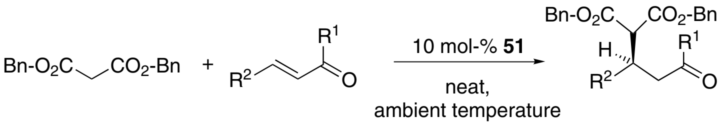


Scheme 4.19

a variety of enones (Scheme 4.20, top) [34a]. The size of the alkyl groups present in the malonate is of crucial importance for high enantioselectivity. In the delicate balance between high enantioselection and maintaining sufficient reactivity, the bis-benzyl malonates proved best. Later the range of C-nucleophiles which could be added to enones was extended to hydroxycoumarins and related compounds (Scheme 4.20, bottom) [34b]. The latter reactions afforded the anticoagulant



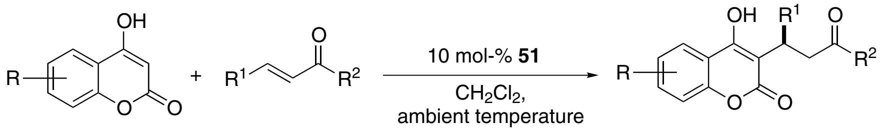
1,4-Addition of malonates (ref. 34a): *catalyst* **51**

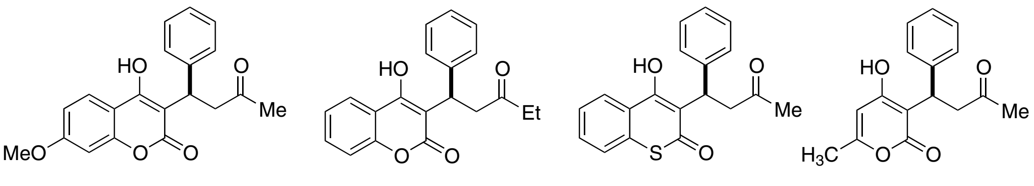


R^1	R^2	Yield (%)	ee (%)
Me	Ph	86	99
Me	2-naphthyl	99	90
Me	4-Cl-Ph	75	98
Me	4-HO-Ph	75	93
Me	2-furyl	75	92
Me	2-pyridyl	95	88
Me	*n*-Bu	61	91
Et	Ph	66	95
Me	CO_2Me	59	59[a]
Cyclohexenone		78	83

[a] Performed at 0 °C.

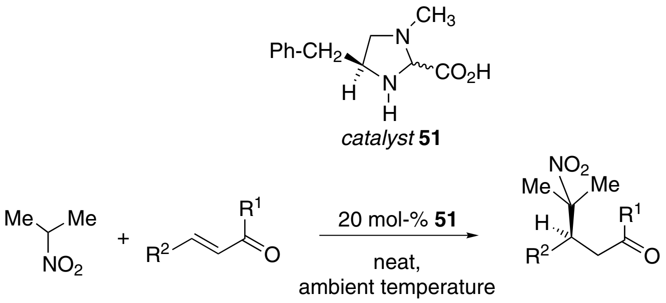
1,4-Addition of hydroxycoumarines and related 1,3-dicarbonyl compounds (ref. 34b):





81 %, 85 % ee | 84 %, 88 % ee | 84 %, 78 % ee | 76 %, 85 % ee

Scheme 4.20

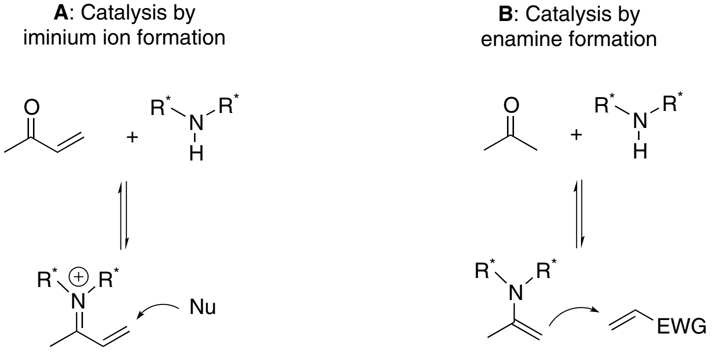


R^1	R^2	Yield (%)	ee (%)
Me	Ph	quant.	79
Et	Ph	69	83
Me	4-Cl-Ph	87	75
Me	4-HO-Ph	86	75

Scheme 4.21

warfarin and derivatives in enantiomerically highly enriched form. Catalyst **51** is similarly efficient in effecting addition of nitroalkanes to enones (Scheme 4.21) [35]. As shown in Scheme 4.21, ee ≥ 75% were observed in several instances; the best results (quant. yield, 79% ee) was achieved in the addition of 2-nitropropane to benzylideneacetone in the presence of 20 mol% catalyst **51**. Recrystallization of the Michael adduct increases the enantiomeric purity to 94–99% ee [35].

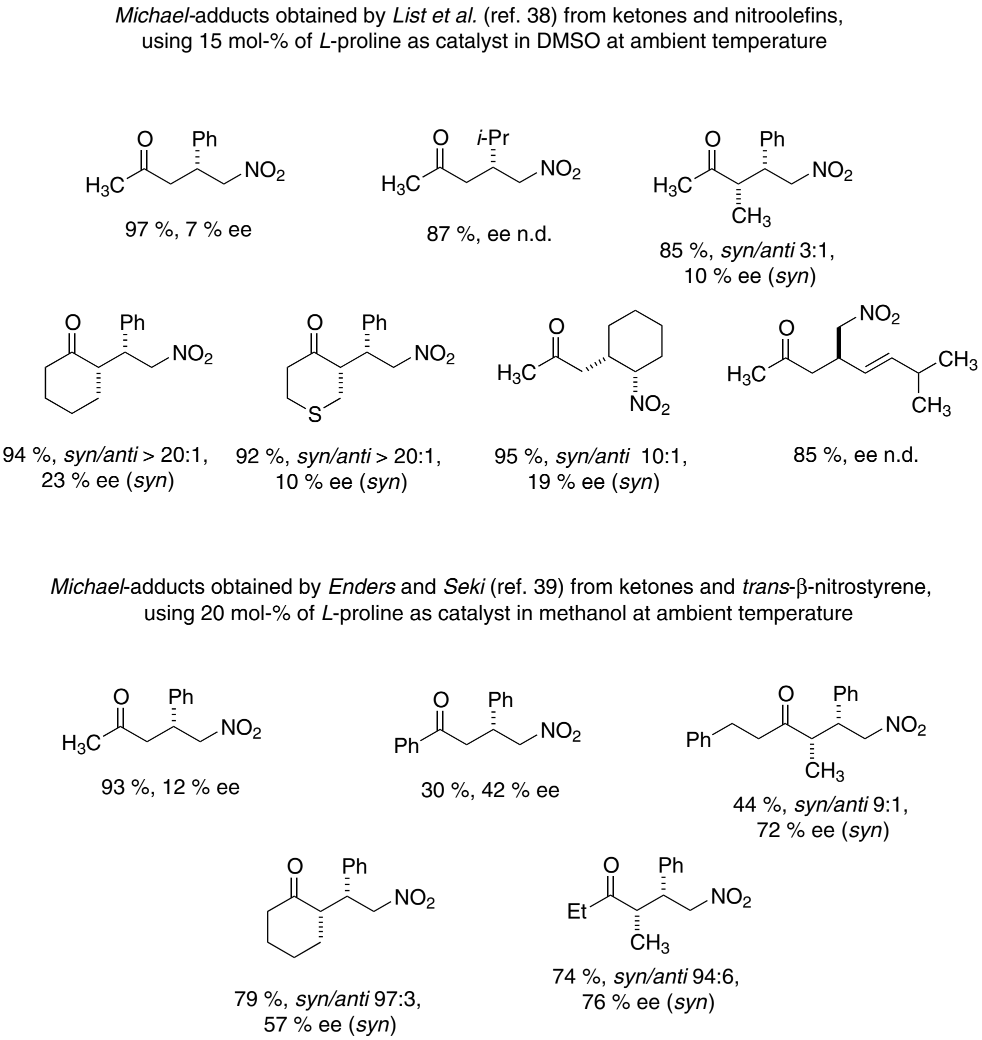
The MacMillan catalysts (**42**, **45**), the Jørgensen catalyst (**51**), and proline itself can promote Michael additions by iminium ion formation with the acceptor enal or enone (**A**, Scheme 4.22). Secondary amines can also activate a carbonyl donor by enamine formation (Scheme 4.22, **B**) [36, 37].



Scheme 4.22

Whereas the examples discussed so far proceed according to the iminium ion mechanism (**A**), amine-catalyzed additions of, e.g., ketones to nitroolefins are effected by intermediate enamine formation (**B**). List et al. were the first to report that L-proline catalyzes the addition of several ketones to nitroolefins (Scheme 4.23). Whereas both the yields and diastereoselectivity were high in DMSO as solvent, the ee did not exceed 23% [38]. A related study of this process by Enders and Seki resulted in identification of methanol as a superior solvent, and enantioselectivity up to 76% was achieved (Scheme 4.23) [39].

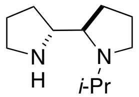
Later work by List and Martin dealt with the use of di- and tripeptides, carrying



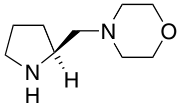
Scheme 4.23

N-terminal L-proline, again in DMSO as solvent [40]. In this study the maximum ee in the addition of acetone to *trans*-2-nitrostyrene was 31%. Alexakis and Andrey successfully employed the bis-pyrrolidine **52** as catalyst for the addition of aldehydes and ketones to *trans*-*β*-nitrostyrene [41], whereas Barbas and Betancort [42] were able to perform the Michael addition of unprotected aldehydes to nitroolefins using the pyrrolidine derivative **53** as catalyst (Scheme 4.24).

2-Aminomethylpyrrolidine catalysts:

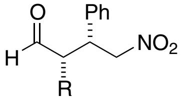


52

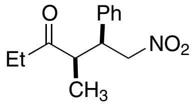


53

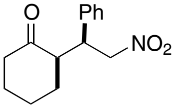
Michael-adducts obtained by *Alexakis* and *Andrey* (ref. 41) from the addition of aldehydes and ketones to *trans*-β-nitrostyrene, using 15 mol-% of **52** as catalyst in $CHCl_3$ at ambient temperature



R = Me: 83 % (0 °C), *syn/anti* 94:6, 85 % ee (*syn*)
R = Et: 82 % (0 °C), *syn/anti* 88:12, 68 % ee (*syn*)
R = *n*-Pr: 98 % (-25 °C), *syn/anti* 96:4, 73 % ee (*syn*)
R = *i*-Pr: 95 %, *syn/anti* 95:5, 68 % ee (*syn*)

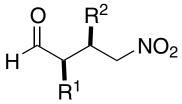


65 %, *syn/anti* 84:16, 76 % ee (*syn*)



74 %, *syn/anti* 95:5, 74 % ee (*syn*)

Michael-adducts obtained by *Barbas* and *Betancort* (ref. 42) from aldehydes and nitroolefins, using 20 mol-% of **53** as catalyst in THF at ambient temperature



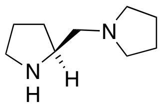
R^1	R^2	Yield [%]	*syn/anti*	ee (*syn*) [%]
Me	Ph	85	90:10	56
Et	Ph	94	86:14	65
n-Bu	Ph	87	85:15	69
i-Pr	Ph	78	92:8	72
i-Pr	2-CF_3-Ph	77	98:2	78
i-Pr	2-thienyl	82	86:14	71
i-Pr	1-naphthyl	67	96:4	75
i-Pr	2-naphthyl	96	89:11	69

Scheme 4.24

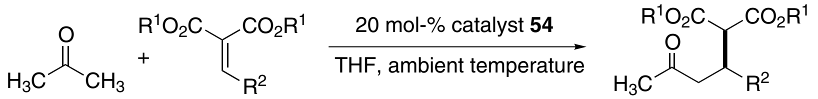
In the study by Alexakis, unsymmetrical ketones (e.g. 2-butanone) yielded mixtures consisting of regioisomers and syn/anti diastereomers with ee of the predominant syn isomers not exceeding 51%. For 3-pentanone and cyclohexanone (Scheme 4.24) Barbas et al. also used the related (*S*)-1-(pyrrolidinylmethyl)-pyrrolidine **54** to catalyze the addition of ketones to alkylidene malonates (Scheme 4.25) [43].

As an additional advantage, the Knoevenagel formation of the alkylidene malonate and the subsequent Michael addition can be performed as a one-pot reaction,

2-Aminomethylpyrrolidine catalyst **54**:

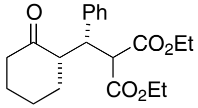


Michael-adducts obtained by *Barbas et al.* (ref. 43) from the addition of acetone to alkylidenemalonates

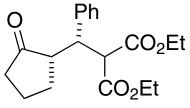


R^1	R^2	Yield [%][a)]	ee [%]
Et	Ph	47 (89)	59
Et	1-naphthyl	31 (72)	64
Et	2-naphthyl	60 (84)	55
Et	2-tolyl	17 (86)	70
Et	2-CF_3-Ph	46 (94)	70
Et	2-furyl	84 (91)	33
Bn	*n*-pentyl	16 (23)	24
Bn	*c*-hexyl	27 (42)	14

[a)]Yields after 4d reaction time,
values in brackets are based on conversion



24 %, *syn/anti* > 20:1,
65 % ee (*syn*)



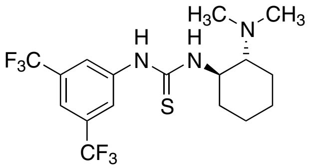
61 %, *syn/anti* 9:1,
53 % ee (*syn*); 55 % ee (*anti*)

Scheme 4.25

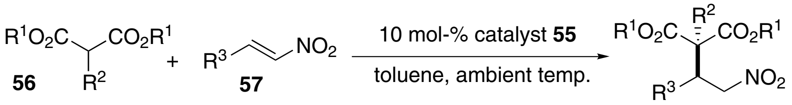
e.g. using benzaldehyde, diethyl malonate, and acetone as the starting materials. It should be noted that catalyst **54** also effects the addition of, e.g., cyclopentanone to *trans-β*-nitrostyrene (78%, syn/anti 4:1, 78% ee syn, 71% ee anti) [43]. For enantioselective addition of malonates or 3-carbomethoxyindanones Brunner and Kimel also employed the cinchona alkaloids quinine, quinidine, cinchonine, and cinchonidine [44]. Enantiomeric excesses were, however, moderate, reaching 43% at best.

The best enantioselectivity in the addition of C-nucleophiles to nitroolefins is that achieved by Takemoto et al. using the bifunctional thiourea-amine catalyst **55** (Scheme 4.26) [45].

Thiourea-amine catalyst **55**:



Michael-adducts obtained by *Takemoto et al.* (ref. 45) from the addition of malonates to nitroolefins



R^1	R^2	R^3	Yield [%]	ee [%]
Et	H	Ph	86	93
Et	H	2,6-$(OMe)_2$-Ph	87	93
Et	H	4-F-Ph	87	92
Et	H	1-naphthyl	95	92
Et	H	2-thienyl	74	90
Et	H	*n*-pentyl	78	81
Et	H	*t*-Bu	88	81
Me	Me	Ph	82	93

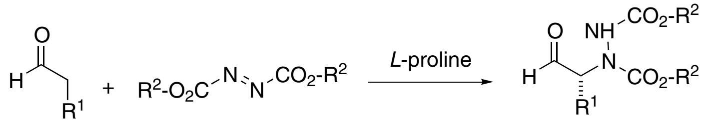
Scheme 4.26

In the presence of 10 mol% of this catalyst, the malonates **56** could be added to several nitroolefins **57** with up to 93% ee. Apolar solvents such as toluene are crucial for high ee values. It is also noteworthy that: (i) good ee can be achieved with catalyst **55** even in the absence of solvents, i.e. with a mixture of the neat starting materials **56** and **57**, and that (ii) the range of Michael donors/acceptors includes aryl- and alkyl-substituted nitroolefins and 2-alkylated malonates.

4.1.1.3 Addition of C-nucleophiles to Azodicarboxylates

C-Nucleophiles have recently been added asymmetrically to azodicarboxylates as Michael-acceptors, resulting in α-amination of the nucleophilic component. Examples of this type of reaction, which is based on activation of the aldehyde or ketone component by enamine formation, are summarized in Scheme 4.27. Please note that this type of reaction is covered in more detail in chapter 7 of this book.

The proline-catalyzed direct asymmetric α-amination of aldehydes was reported in 2002 by both List [46] and Jørgensen [47]. As shown in Scheme 4.27 a variety of azodicarboxylates **58** can be added to aldehydes, affording the α-aminated products **59** in very good yields and with excellent ee. The experimental procedures are, furthermore, very convenient. The primary addition products **59** are configurationally unstable and are usually either reduced to the corresponding alcohols **60** (e.g.



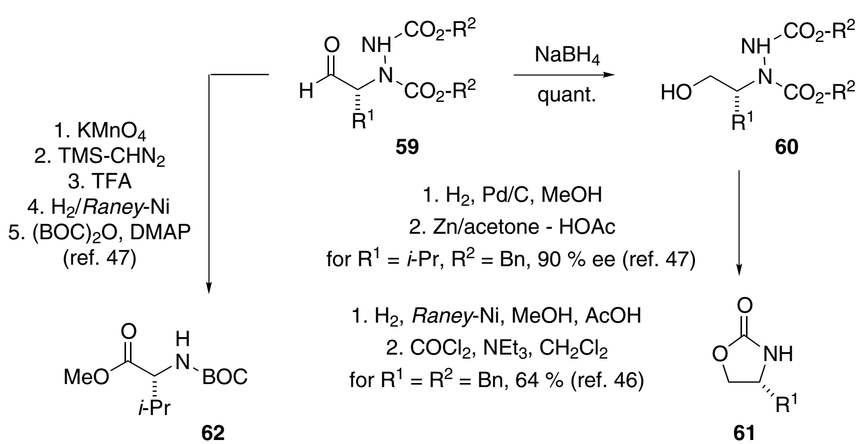
58 **59**

List (ref. 46):

R^1 = Me, *n*-Pr, *i*-Pr, *n*-Bu, Bn; R^2 = *t*-Bu, Bn; 10 mol-% catalyst, solvent acetonitrile
yields: 93 %-quant.; 86-92 % ee (20 °C), > 95 % ee (0 °C)

Jørgensen et al. (ref. 47):

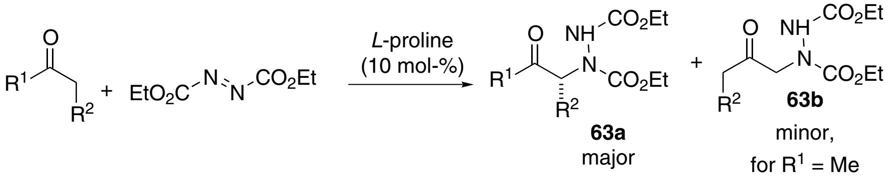
R^1 = Me, Et, *i*-Pr, *t*-Bu, allyl, Bn; R^2 = Et, Bn; 10 mol-% catalyst, solvent dichloromethane
yields: 67-92 %; 89-95 % ee (20 °C)



62 **61**

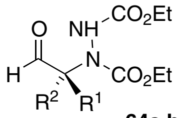
Scheme 4.27

Jørgensen et al. (ref. 48a):

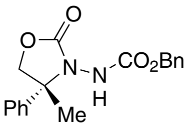


R^1	R^2	Major:Minor **63a**:**63b**	Yield [%] **63a**+**63b**	ee **63a** [%]
-$(CH_2)_4$-		- - - - -	67	84
Me	Me	91:9	80	95
Me	Et	81:19	77	98
Me	Bn	82:18	92	98
Me	*i*-Pr	76:24	69	99
Et	Me	- - - - -	79	94

Bräse et al. (ref. 48b):



64a,b



64a: R^1 = Me, R^2 = 2-naphthyl: 54 %, 86 % ee
64b: R^1 = Me, R^2 = Ph: 62 %, 80 % ee

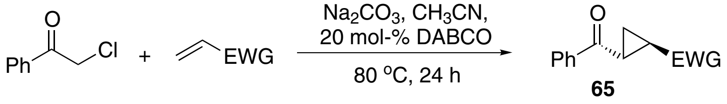
64c: 83 %, 81 % ee

Scheme 4.28

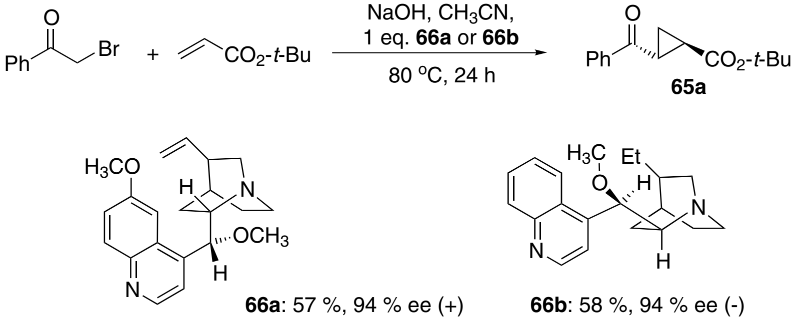
for ee analysis) or are reacted further in a few steps to, e.g., the Evans auxiliaries **61** or protected amino acids such as **62** (Scheme 4.27). Jørgensen et al. extended the α-amination reaction to ketones [48a]. As shown in Scheme 4.28, regioselectivity of ca 8:2 to 9:1 (**63a**:**63b**) in favor of the amination of the more substituted α-position was achieved, the ee of the major products (**63a**) being in the range 84–99%. Bräse et al. reported the α-amination of α-disubstituted aldehydes, using L-proline or L-azetidinecarboxylic acid as catalysts [48b]. L-Proline generally afforded higher enantioselectivity, up to 86% ee, as for the addition product **64a** shown in Scheme 4.28. On reduction of the aldehyde cyclization affords oxazolidinones such as **64c**.

4.1.1.4 **Cyclopropanation of Enoates with Phenacyl Halides**

Gaunt et al. recently reported that tertiary amines such as DABCO catalyze the reaction of enoates, enones, enals, α,β-unsaturated amides, nitriles, and sulfones



EWG	Yield [%]	*trans:cis*
CO_2-*t*-Bu	69	> 95:5
CO-CH_3	82	> 95:5
SO_2-Ph	63	> 95:5

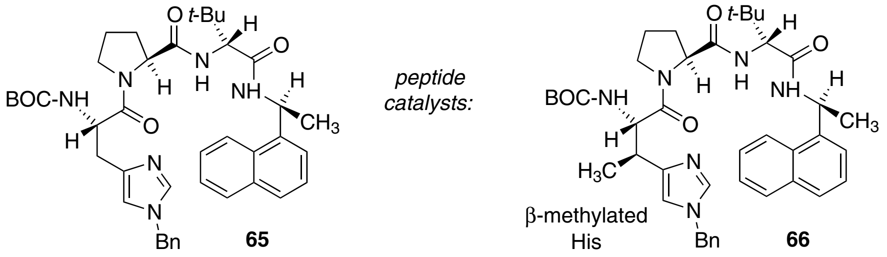


Scheme 4.29

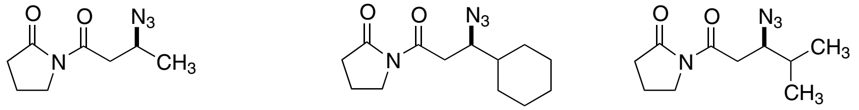
with α-halo carbonyl compounds in the presence of base (for example NaOH or Na_2CO_3) to yield cyclopropanes **65** in good yields and with high trans selectivity (Scheme 4.29) [49a]. This cyclopropanation of α,β-unsaturated carbonyl compounds is believed to proceed *via* the corresponding ammonium ylides and can be performed (i) starting from the pre-formed quaternary ammonium salts as the ylide precursor, (ii) in a one-pot fashion using stoichiometric amounts of DABCO and base, or (iii) with stoichiometric amounts of base and just 20 mol% DABCO. Examples of the latter (non-enantioselective) process are shown in Scheme 4.29. By use of chiral tertiary amines such as the alkaloid derivatives **66a**,**b**, shown in Scheme 4.29, the cyclopropane **65a** was obtained in up to 94% ee. This asymmetric cyclopropanation requires one equivalent of the chiral bases **66a**,**b**. The most recent variants of this method require only catalytic amounts of chiral cinchona bases and afford up to 97% ee [49b, c].

4.1.2
Intermolecular Michael Addition of N- and O-nucleophiles

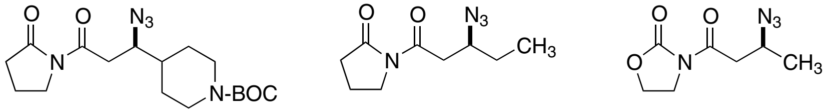
The Michael addition of *N*-nucleophiles to α,β-unsaturated carbonyl compounds is of obvious synthetic importance, e.g. for the preparation of β-amino acids [50a]. Several metal-containing catalysts have been devised, e.g. the chiral Al-salen



β–Azido imides prepared by addition of TMS-N_3 to α,β-unsaturated (*E*)-imides, catalyzed by 2.5 mol-% of the peptide catalyts **65** and **66**:
(25 °C, if not stated otherwise)



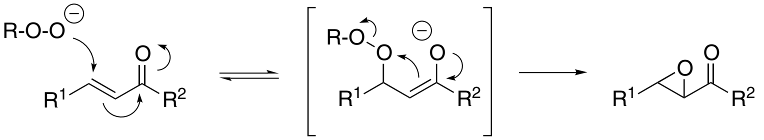
catalyst **65**:	97 %, 63 % ee	79 %, 85 % ee	84 %, 82 % ee
catalyst **66**:	90 %, 78 % ee	88 %, 89 % ee	89 %, 84 % ee
	90 %, 86 % ee (-10 °C)	65 %, 92 % ee (-10 °C)	75 %, 90 % ee (-10 °C)



catalyst **65**:	85 %, 71 % ee	91 %, 71 % ee	85 %, 45 % ee
catalyst **66**:	95 %, 80 % ee	95 %, 77 % ee	82 %, 71 % ee
	79 %, 87 % ee (-10 °C)	83 %, 85 % ee (-10 °C)	44 %, 78 % ee (-10 °C)

Scheme 4.30

complexes by Jacobsen et al. that catalyze the addition of hydrazoic acid to *α*,*β*-unsaturated imides with up to 97% ee [50b]. In 2000 Miller et al. reported the first highly efficient and selective organocatalysts for this purpose, the tripeptide **65** (Scheme 4.30) [51a]. On the basis of conformational studies it was assumed that rigidification of the *N*-terminal histidine residue by a *β*-substituent should be beneficial. In fact, and as summarized in Scheme 4.30, the *β*-methylated peptide **66** effects addition of TMS-N_3 to several unsaturated imides with even better enantioselectivity [51b]. Typically, 2.5 mol% peptide catalysts **65** or **66** were employed, and enantiomeric excesses up to 92% was achieved (Scheme 4.30). The *β*-azido imides are readily converted to *β*-amino acids by hydrogenation/BOC-protection



Scheme 4.31

and hydrolysis [51a]. Alternatively, cycloaddition with an alkene/alkyne leads to triazolines/triazoles [51b].

In contrast with metal-complex catalyzed transformations [52], enantioselective organocatalyzed intermolecular conjugate additions of *O*-nucleophiles seem to be limited to peroxides such as hydrogen peroxide or *tert*-butyl hydroperoxide. In these reactions the primary addition product, a β-peroxy enolate, reacts further to yield an epoxide (Scheme 4.31). Consequently, reactions of this type are covered in Section 10.2 "Epoxidation of Enones and Enoates".

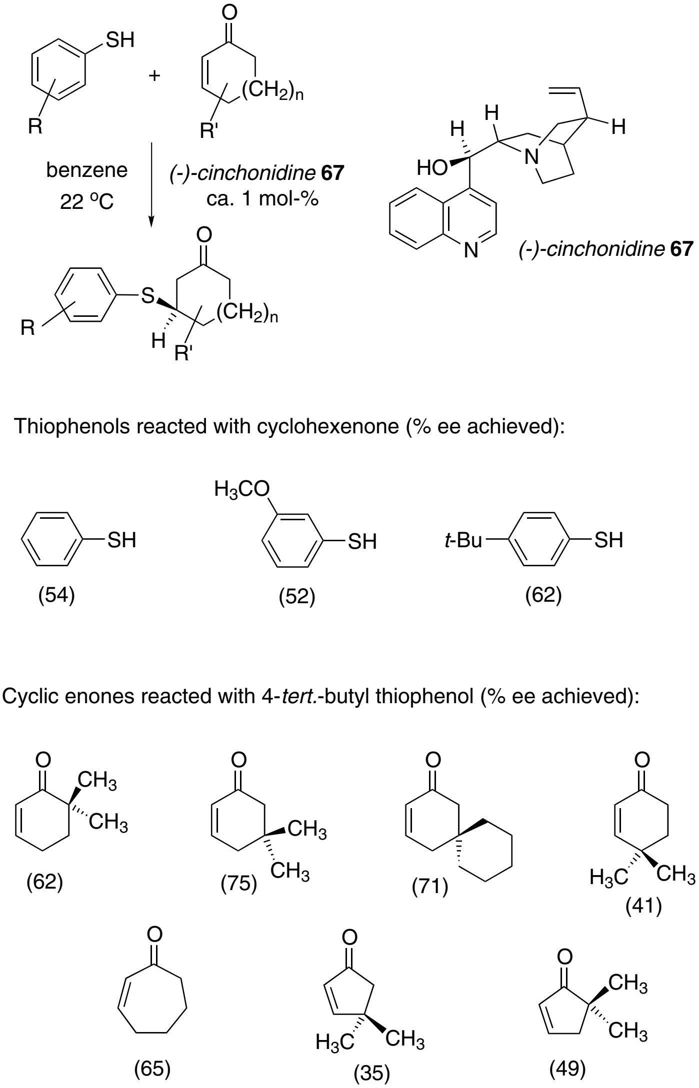
4.1.3
Intermolecular Michael Addition of S- and Se-nucleophiles

As early as 1977, Wynberg et al. reported that under the influence of less than one mol% (−)-quinine as chiral base, a variety of thiophenols and benzyl mercaptan can be added to cyclohexenone in very good yield and enantiomeric excesses up to 46% [53a]. Subsequent in-depth studies by Hiemstra and Wynberg resulted in a detailed mechanistic picture of the chiral-base catalyzed addition of thiophenols to cyclic enones and provided enantiomeric excesses up to 75%, e.g. by using (−)-cinchonidine **67** as the catalytic base (Scheme 4.32) [53b].

Addition of the thiophenolate anion to the β-carbon atom of the enone is the chirality-determining step; it is, at the same time, rate-determining. The transition state is a ternary complex comprising the catalytic base in the protonated form, the thiophenolate anion, and the enone. The last is activated to nucleophilic attack by hydrogen-bonding to the catalysts β-hydroxy group. The chiral cinchona bases thus act as *bifunctional* catalysts.

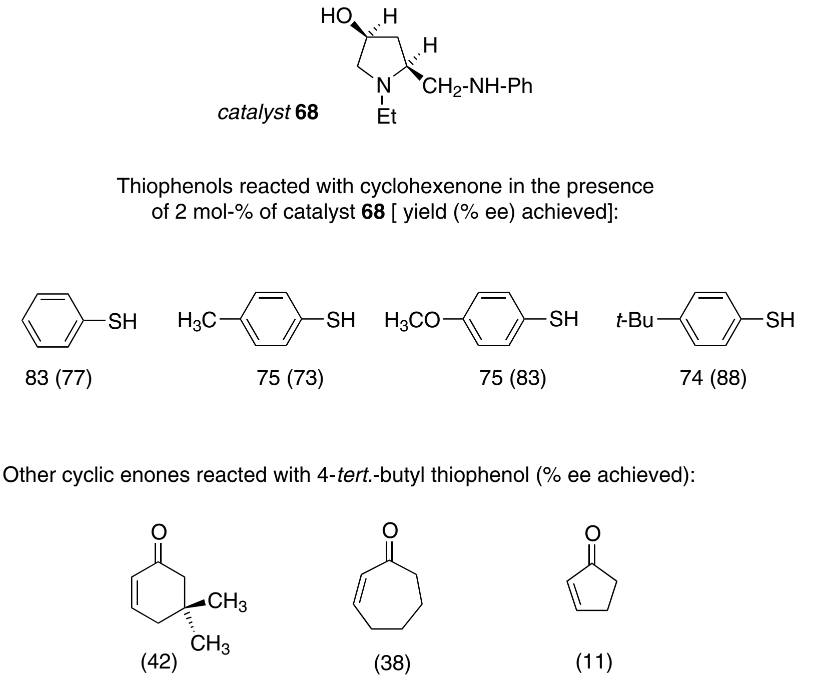
In related studies, Mukaiyama et al. identified 2-(anilinomethyl)-1-ethyl-4-hydroxypyrrolidine **68** as a very efficient catalyst of the addition of thiophenols to cycloalkenones [54a–c]. This catalyst, which was prepared from hydroxyproline in five steps, afforded up to 88% ee in the addition of thiophenols to cyclohexenone (Scheme 4.33).

The cinchonidine-catalyzed addition of 4-*tert*-butylthiophenol reported by Wynberg and Hiemstra has also been used for kinetic resolution of racemic 5-methyl-2-cyclohexen-1-one: At an enone/thiophenol ratio of 2:1, the remaining enone had an optical purity of 36% [54]. A similar procedure was employed by Asaoka et al. for kinetic resolution of 5-trimethylsilyl-2-cyclohexen-1-one, affording 50% of the trans adduct (57% ee, enantiomerically pure after recrystallization) with 41% of the starting enone (59% ee) [55a].



Scheme 4.32

Whereas the results summarized in Scheme 4.32 were achieved under homogeneous reaction conditions, Colonna et al. reported the use of chiral phase-transfer catalysts for asymmetric addition of benzyl mercaptan and thiophenols to cyclohexenone and derivatives [55b]. The best result was 85% yield and 36% enantiomeric excess in the addition of thiophenol to cyclohexenone, catalyzed by ca 0.4 mol% *N*-(*o*-nitrobenzyl)quininium chloride at 25 °C. In this experiment, CCl_4 served as solvent and solid KF as the base. Finally, Aida et al. reported in 1996 that chiral

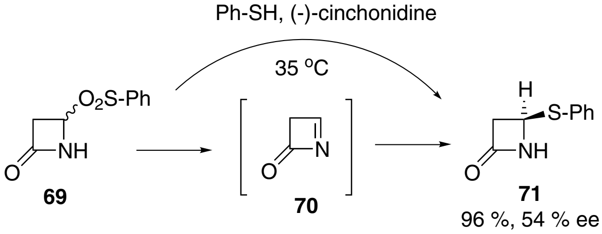


Scheme 4.33

N-alkylated porphyrins can also serve as catalytic bases in the asymmetric addition of thiophenols to enones [55c]. In the most selective example (addition of 2-methylthiophenol to cyclohexenone), 55% ee was achieved.

As early as 1977 Pracejus et al. investigated alkaloid-catalyzed addition of thiols to α-phthalimido acrylates, methylene azlactones, and nitroolefins [56a]. In the former approach, protected cysteine derivatives were obtained with up to 54% ee. Mukaiyama and Yamashita found that addition of thiophenol to diisopropyl maleate in the presence of cinchonine (10 mol%) proceeds in 95% yield and that the product, (*S*)-phenylthiosuccinate, was formed with 81% ee [56b]. The latter Michael adduct was used as starting material for preparation of (*R*)-(+)-3,4-epoxy-1-butanol. In the course of an asymmetric total synthesis of (+)-thienamycin Ikegami et al. studied the substitution of the phenylsulfonyl substituent in the azetidinone **69** by thiophenol in the presence of cinchonidine (Scheme 4.34) [56c]. This substitution probably proceeds *via* the azetinone **70**. In this reaction the phenylthioazetidinone **71** was obtained in 96% yield and 54% ee. Upon crystallization, the optically pure substitution product **71** was obtained from the mother liquor [56c].

Kobayashi et al. studied the alkaloid-catalyzed addition of thioglycolic acid to *trans*-β-nitrostyrenes and other nitroolefins [57a]. Under carefully controlled reaction conditions 58% ee was achieved in the addition of thioglycolic acid to (unsubstituted) *trans*-β-nitrostyrene and 37% ee for a non-aromatic nitroolefin. Similar



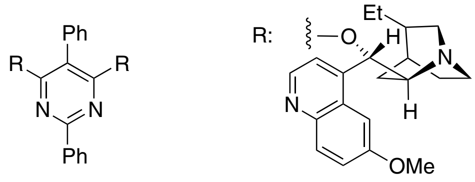
Scheme 4.34

enantioselectivity was achieved by Wynberg et al. in the alkaloid-catalyzed addition of thiocarboxylic acids to cyclohexenones [57b] and enoates [57c]. Interestingly, it was observed in the study by Kobayashi et al. [57a] that not only did the rate of reaction and extent of asymmetric induction vary with catalyst/substrate ratio, but the *sense* of induction also. This observation stresses the importance of higher aggregates in this particular reaction and pinpoints an important condition for optimization of other, related, processes. The use of acrylonitrile–cinchona alkaloid copolymers by the same authors in the addition of benzyl mercaptan to *trans-β*-nitrostyrene resulted in low enantiomeric excess (≤ 18%) [57d]. Similar results were obtained by Hodge et al. [57e]. The latter authors also studied the addition of thiophenol and thiobenzoic acid to cyclohexenone in the presence of polymer-bound cionchone alkaloids (ee max. 45%) [57e]. The soluble PEG-bound cinchona alkaloid catalysts prepared by Benaglia et al. afforded 22% ee in the addition of thiophenol to cyclohexenone [57f]. Sera et al. investigated the effect of high pressure on the enantioselectivity of addition of thiophenol to cyclohexenones [58]. As a general trend, enantioselectivity *decreased* with increasing pressure. For example, addition of 4-*tert*-butyl thiophenol to cyclohexenone was reported to occur at atmospheric pressure with 50% ee [ca. 1 mol% quinine (**3a** Scheme 4.3)] as catalyst, in toluene) whereas 41% ee was obtained at 900 MPa. This general trend was interpreted in terms of the pressure susceptibility of the diastereomorphic transition states leading to the enantiomeric products [58].

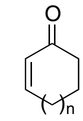
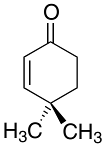
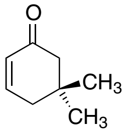
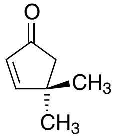
The highest enantioselectivity (up to >99%) yet achieved in the addition of S-nucleophiles to enones was reported in 2002 by Deng et al. [59]. By systematic screening of monomeric and dimeric cinchona alkaloid derivatives they identified the dihydroquinidine–pyrimidine conjugate $(DHQD)_2PYR$ (**72**, Scheme 4.35) as the most effective catalyst. This material is frequently used in the Sharpless asymmetric dihydroxylation and is commercially available. Screening of several aromatic thiols resulted in the identification of 2-thionaphthol as the nucleophile giving best yields and enantioselectivity. Examples for the $(DHQD)_2PYR$-catalyzed addition of 2-thionaphthol to enones are summarized in Scheme 4.35.

There seem to be very few examples of organocatalytic Michael additions of Se-nucleophiles, and these are limited to the addition of selenophenols to enones (Scheme 4.36) [3, 60]. As shown in the scheme, Wynberg and Pluim achieved

catalyst **72** [$(DHDQ)_2PYR$]:

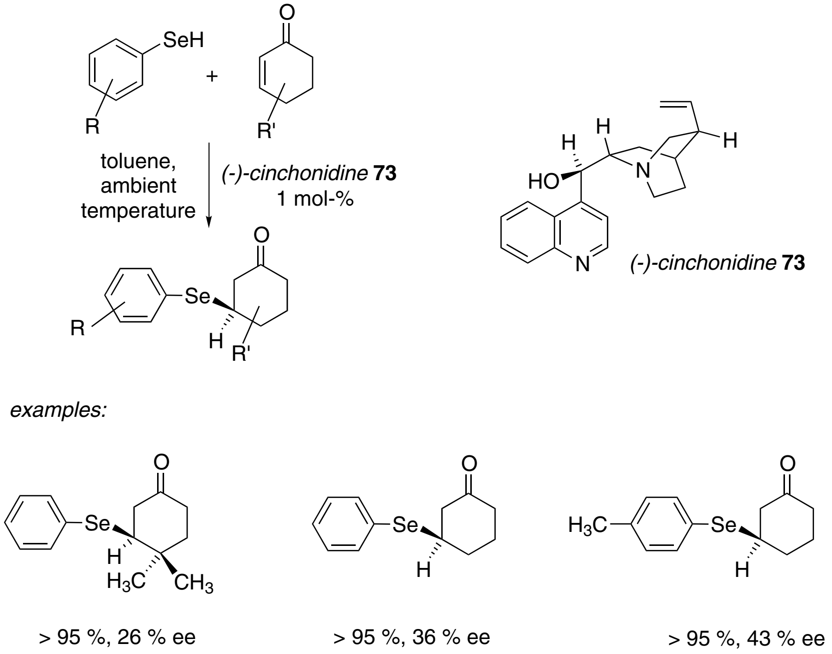


addition of 2-thionaphthol, -60 - -50 °C,
1 mol-% catalyst **72**

Enone		Yield [%]	ee [%]
	n = 0	55	41
	n = 1	77	94
	n = 2	86	97
	n = 3	82	>99
	n = 4	91	97
		88	95
		88	93
		71	92

Scheme 4.35

moderate ee by using (−)-cinchonidine **73** as the chiral base. The enantiomeric purity of the crystalline Michael-adducts could be significantly enhanced by repeated recrystallization (> 85% ee). According to Wynberg and Pluim, the selenoketones thus obtained could be converted into enantiomerically enriched allylic alcohols by diastereoselective ketone reduction then oxidative elimination of the arylselenyl ether moiety [60].



Scheme 4.36

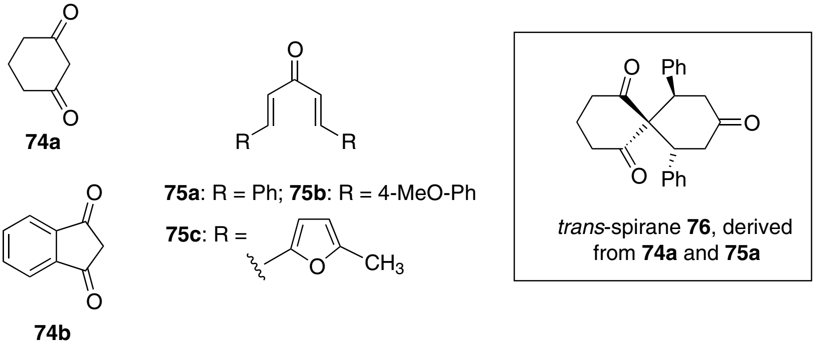
4.2
Intramolecular Michael Addition

4.2.1
Intramolecular Michael Addition of C-nucleophiles

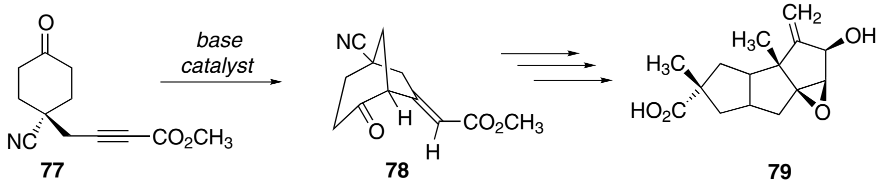
Only three examples of intramolecular organocatalyzed and enantioselective Michael additions of C-nucleophiles seem to have been reported in the literature. In 1979 Wynberg and ten Hoeve reported the (−)-quinine-catalyzed double Michael addition of the 1,3-diones **74a**,**b** to the 1,5-disubstituted pentadien-3-ones **75a–c** (Scheme 4.37) [61].

Both the cis- and the trans-disubstituted spiranes resulted, in different ratios, depending on the reaction conditions. Clearly, the trans spiranes are chiral. The first conjugate addition to the Michael acceptors **75a–c** is intermolecular in nature and defines the sense of chirality at the first chiral center. Subsequent intramolecular ring closure to the spiranes **76** defines the cis or trans configuration of the product. When cyclohexane-1,3-dione (**74a**) was reacted with dibenzalacetone (**75a**) in the presence of ca 5 mol% (−)-quinine (**3a**, Scheme 4.3), a 2.5:1 trans/cis mixture resulted, with the trans isomer **76** having optical purity of ca 30% (Scheme 4.37) [61] (the absolute configuration of the predominant enantiomer was not assigned).

The bicyclo[3.2.1]octane *rac*-**78** is an intermediate in the synthesis of hirsutic acid (*rac*-**79**), published in 1979 by Trost et al. (Scheme 4.38) [62]. It is prepared



Scheme 4.37



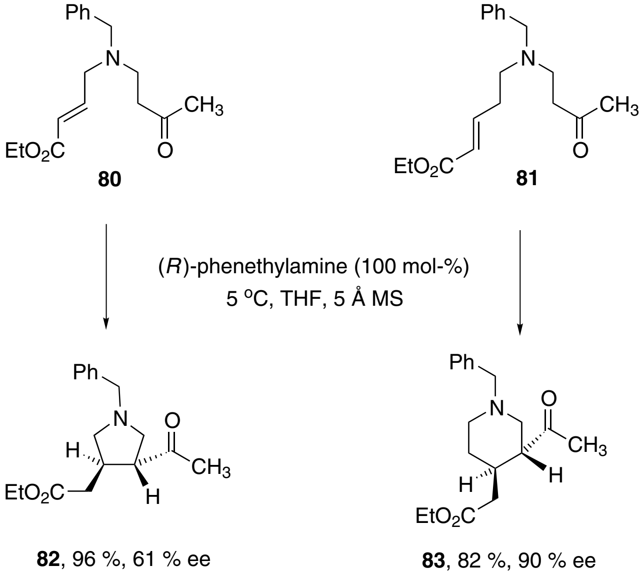
Scheme 4.38

by base-catalyzed intramolecular Michael-reaction of the achiral cyclohexanone **77** (Scheme 4.38). When the cyclization of **77** is induced by (−)-quinine (**3a**, Scheme 4.3), the two enantiomers of the bicyclic compound **78** were obtained in a ratio of 65:35 [62] (the absolute configuration of the predominant enantiomer was not assigned).

The third example is summarized in Scheme 4.39. Momose et al. used equimolar amounts of enantiomerically pure (*R*)- or (*S*)-phenethylamine to induce cyclization of the keto enoates **80** and **81** [63]. The trans-configured pyrrolidine (**82**) and piperidine (**83**) building blocks were obtained in quite satisfactory chemical yields and with enantiomeric excesses up to 90%.

4.2.2
Intramolecular Michael Addition of O-nucleophiles

Ishikawa et al. employed the (−)-quinine-catalyzed cyclization of the *o*-tigloylphenol **87** and the *o*-angeloylphenol **86** in the synthesis of the potential anti-HIV-active natural product (+)-calanolide A (**86**, Scheme 4.40) [64, 65]. In a model study it was first shown that the *o*-tigloylphenol **84** (Scheme 40, top) can be cyclized by (−)-quinine to afford a 1:1 mixture of the cis product **85a** (87% ee) and the trans product **85b** (racemic) [64]. The analogous use of (+)-quinidine gave rise to the enantiomeric products, again with the trans product being racemic, and with 75% ee of the cis product *ent*-**85a**. A careful study of solvent effects led to identification of chlorobenzene as the optimum medium. As shown in Scheme 40 (bottom), cyclization of the *o*-tigloylphenol **87** in chlorobenzene afforded an 8:2-mixture of



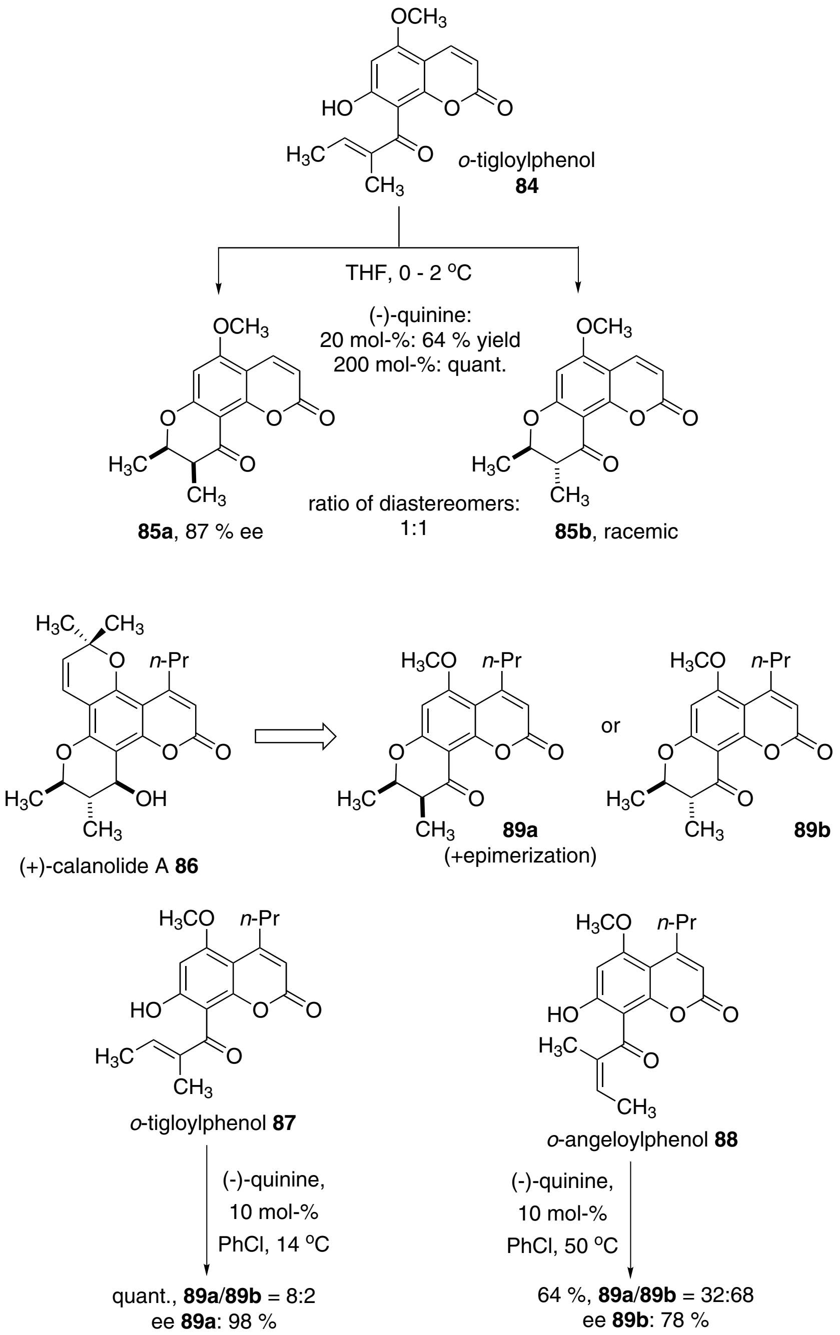
Scheme 4.39

the cis (**89a**) and trans (**89b**) precursors of (+)-calanolide A (**86**), in which the cis product **89a** was formed with 98% ee [65]. Under similar conditions, the *o*-angeloylphenol **88** gave a 32:68 cis (**89a**) to trans (**89b**) mixture, with 78% ee of the trans product **89b** [65]. See ref. 66 for a recent example of an alkaloid-catalyzed asymmetric chromane synthesis by Merschaert et al.

There appear to be no reports of asymmetric organocatalytic intramolecular Michael additions of N-, S- or Se-nucleophiles.

Conclusions

Asymmetric Michael additions catalyzed by chiral bases or phase-transfer catalysts based on alkaloids are among the first catalytic asymmetric transformations ever achieved – the earliest examples date back to the 1970s. In these pioneering studies, enantiomeric excesses were not usually in a range suitable for preparative applications – values "in the eighties" were exceptional and achieved only rarely. The past 5–10 years, however, have seen *dramatic* advances in the field of organocatalyzed Michael additions. Conjugate additions of C-nucleophiles to a variety of α,β-unsaturated carbonyl compounds and to nitroolefins can currently be performed with readily available organocatalysts operating by intermediate formation of iminium cations or enamines. Enantiomeric excesses exceeding 90–95% have been achieved in numerous reactions. Many synthetically extremely useful Michael adducts have been made readily available in enantiomerically pure form by use of



OCH3
HO
O
O
H3C
O
CH3
o-tigloylphenol
84
THF, 0 - 2 °C
(-)-quinine:
20 mol-%: 64 % yield
200 mol-%: quant.
ratio of diastereomers:
1:1
85a, 87 % ee
85b, racemic
H3C CH3
n-Pr
OH
(+)-calanolide A 86
H3CO
or
89a
(+epimerization)
89b
o-tigloylphenol 87
o-angeloylphenol 88
(-)-quinine,
10 mol-%
PhCl, 14 °C
PhCl, 50 °C
quant., 89a/89b = 8:2
ee 89a: 98 %
64 %, 89a/89b = 32:68
ee 89b: 78 %

Scheme 4.40

the two types of organocatalysis described above. Chiral bases and phase-transfer catalysts (PTC) have also been applied in the addition of both C- and hetero-nucleophiles, and enantioselectivity > 95% ee has been achieved. It is probable that the further optimization of existing types of base and PTC will provide even greater generality. In this context it is particularly noteworthy that for the conjugate addition of azide to α,β-unsaturated imides, peptide catalysts have been shown to afford excellent yields and enantioselectivity. This class of compounds is particularly suitable for (combinatorial) adaptation to a given catalytic task [67]. Potential for further improvement of organocatalytic Michael additions may be seen in shortening the reaction times. This aspect (too) surely warrants further research effort.

References

1 For recent and general reviews on catalytic asymmetric Michael additions, see: (a) N. Krause, A. Hoffmann-Röder, *Synthesis* **2001**, 171–196; (b) M. P. Sibi, S. Manyem, *Tetrahedron* **2000**, *56*, 8033–8061.

2 H. Wynberg, R. Helder, *Tetrahedron Lett.* **1975**, *46*, 4057–4060.

3 For a review on the use of alkaloids in asymmetric organocatalysis, see: H. Wynberg, *Topics Stereochem.* **1986**, *16*, 87–129.

4 K. Hermann, H. Wynberg, *J. Org. Chem.* **1979**, *44*, 2238–2244.

5 R. Alvarez, M.-A. Hordin, C. Cavé, J. d'Angelo, P. Chaminade, *Tetrahedron Lett.* **1999**, *40*, 7091–7094.

6 (a) N. Kobayashi, K. Iwai, *J. Am. Chem. Soc.* **1978**, *100*, 7071–7072; (b) M. Inagaki, J. Hiratake, Y. Yamamoto, J. Oda, *Bull. Chem. Soc. Jpn.* **1987**, *60*, 4121–4126.

7 B. Långström, G. Bergson, *Acta Chem. Scand.* **1973**, *27*, 3118–3132.

8 R. S. E. Conn, A. V. Lovell, S. Karady, L. M. Weinstock, *J. Org. Chem.* **1986**, *51*, 4710–4711.

9 T. Ooi, T. Miki, M. Taniguchi, M. Shiraishi, M. Taakeuchi, K. Maruoka, *Angew. Chem.* **2003**, *115*, 3926–3928; *Angew. Chem. Int. Ed.* **2003**, *42*, 3796–3798.

10 F.-Y. Zhang, E. J. Corey, *Org. Lett.* **2000**, *2*, 1097–1100.

11 F.-Y. Zhang, E. J. Corey, *Org. Lett.* **2001**, *3*, 639–641.

12 E. J. Corey, M. C. Noe, F. Xu, *Tetrahedron Lett.* **1998**, *39*, 5347–5350.

13 S. Arai, R. Tsuji, A. Nishida, *Tetrahedron Lett.* **2002**, *43*, 9535–9537.

14 T. Shiuguchi, Y. Fukuta, Y. Akachi, A. Sekine, T. Ohshima, M. Shibasaki, *Tetrahedron Lett.* **2002**, *43*, 9539–9543.

15 D. Ma, K. Cheng, *Tetrahedron: Asymmetry* **1999**, *10*, 713–719.

16 T. Perrard, J.-C. Plaquevent, J.-R. Desmurs, D. Hébrault, *Org. Lett.* **2000**, *2*, 2959–2962.

17 S. Colonna, H. Hiemstra, H. Wynberg, *J. Chem. Soc., Chem. Commun.* **1978**, 238–239.

18 E. J. Corey, F.-Y. Zhang, *Org. Lett.* **2000**, *2*, 4257–4259.

19 P. Bakó, T. Kiss, L. Töke, *Tetrahedron Lett.* **1997**, *41*, 7259–7262.

20 P. Bakó, T. Novák, K. Luidányi, B. Pete, L. Töke, G. Keglevich, *Tetrahedron: Asymm.* **1999**, *10*, 2373–2380.

21 P. Bakó, A. Szöllösy, P. Bombicz, L. Töke, *Synlett* **1997**, 291–292.

22 M. Yamaguchi, T. Shiraisi, M. Hirama, *Angew. Chem.* **1993**, *105*, 1243–1245; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1176–1178.

23 M. Yamaguchi, T. Shiraisi, M. Hirama, *J. Org. Chem.* **1996**, *61*, 3520–3530.

24 A. Kawara, T. Taguchi, *Tetrahedron Lett.* **1994**, *35*, 8805–8808.

25 M. Yamaguchi, T. Shiraishi,

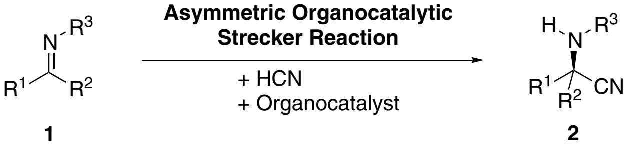
Y. Igarashi, M. Hirama, *Tetrahedron Lett.* **1994**, *35*, 8233–8236.
26 M. Yamaguchi, Y. Igarashi, R. S. Reddy, T. Shiraishi, M. Hirama, *Tetrahedron* **1997**, *53*, 11223–11236.
27 S. Hanessian, V. Pham, *Org. Lett.* **2000**, *2*, 2975–2978.
28 K. A. Ahrendt, C. J. Borths, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2000**, *122*, 4243–4244. For the synthesis of polymer-bound derivatives of the *MacMillan* catalyst and applications in *Diels–Alder* reactions, see: M. Benaglia, G. Celentano, M. Cinquini, A. Puglisi, F. Cozzi, *Adv. Synth. Catal.* **2002**, *344*, 149–152; S. A. Selkälä, J. Tois, P. M. Pihko, A. M. P. Koskinen, *Adv. Synth. Catal.* **2002**, *344*, 941–945.
29 W. S. Jen, J. J. M. Wiener, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2000**, *122*, 9874–9875.
30 N. A. Paras, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2001**, *123*, 4370–4371.
31 J. F. Austin, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2002**, *124*, 1172–1173.
32 N. A. Paras, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2002**, *124*, 7894–7895.
33 S. P. Brown, N. C. Goodwin, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2003**, *125*, 1192–1194.
34 (a) N. Halland, P. S. Aburel, K. A. Jørgensen, *Angew. Chem.* **2003**, *115*, 685–689; *Angew. Chem. Int. Ed.* **2003**, *42*, 661–665; (b) N. Halland, T. Hansen, K. A. Jørgensen, *Angew. Chem.* **2003**, *115*, 5105–5107; *Angew. Chem. Int. Ed.* **2003**, *42*, 4955–4957.
35 N. Halland, R. G. Hazell, K. A. Jørgensen, *J. Org. Chem.* **2002**, *67*, 8331–8338.
36 For diastereoselective additions of preformed chiral enamines to *Michael*-acceptors, see: D. Seebach, M. Missbach, G. Calderari, M. Eberle, *J. Am. Chem. Soc.* **1990**, *112*, 7625–7638; S. J. Blarer, D. Seebach, *Chem. Ber.* **1983**, *116*, 2250–2260; S. Yamada, K. Hiroi, K. Achiwa, *Tetrahedron Lett.* **1969**, 4233–4236.
37 For a highlight on asymmetric organocatalysis by proline and other low-molecular weight organic molecules, see: H. Gröger, J. Wilken, *Angew. Chem.* **2001**, *113*, 545–548; *Angew. Chem. Int. Ed.* **2001**, *40*, 529–532.
38 B. List, P. Pojarliev, H. J. Martin, *Org. Lett.* **2001**, *3*, 2423–2425.
39 D. Enders, A. Seki, *Synlett* **2002**, 26–28.
40 H. J. Martin, B. List, *Synlett* **2003**, 1901–1902.
41 A. Alexakis, O. Andrey, *Org. Lett.* **2002**, *4*, 3611–3614.
42 J. M. Betancort, C. F. Barbas III, *Org. Lett.* **2001**, *3*, 3737–3740.
43 J. M. Betancort, K. Sakthivel, R. Thayumanavan, C. F. Barbas III, *Tetrahedron Lett.* **2001**, *42*, 4441–4444.
44 H. Brunner, B. Kimel, *Monatsh. Chem.* **1996**, *127*, 1063–1072.
45 T. Okino, Y. Hoashi, Y. Takemoto, *J. Am. Chem. Soc.* **2003**, *125*, 12672–12673.
46 B. List, *J. Am. Chem. Soc.* **2002**, *124*, 5656–5657.
47 A. Bøgevig, K. Juhl, N. Kumaragurubaran, W. Zhuang, K. A. Jørgensen, *Angew. Chem.* **2002**, *114*, 1868–1871; *Angew. Chem. Int. Ed.* **2002**, *41*, 1790–1793.
48 (a) N. Kumaragubaran, K. Juhl, W. Zhuang, A. Bøgevig, K. A. Jørgensen, *J. Am. Chem. Soc.* **2002**, *124*, 6254–6255; (b) H. Vogt, S. Vanderheiden, S. Bräse, *J. Chem. Soc., Chem. Commun.* **2003**, 2448–2449.
49 (a) C. D. Papageorgiou, S. V. Ley, M. J. Gaunt, *Angew. Chem.* **2003**, *115*, 852–855; *Angew. Chem. Int. Ed.* **2003**, *42*, 828–831. (b) N. Bremayer, S. C. Smith, S. V. Ley, M. J. Gaunt, *Angew. Chem.* **2004**, *116*, 2735–2738; *Angew. Chem. Int. Ed.* **2004**, *43*, 2681–2684. (c) C. D. Papageorgiou, M. A. Cubillo de Dios, S. V. Ley, M. J. Gaunt, *Angew. Chem.* **2004**, *116*, 4741–4744; *Angew. Chem. Int. Ed.* **2004**, *43*, 4641–4644.
50 (a) E. Juaristi (Ed.), *Enantioselective Synthesis of β-Amino Acids*, Wiley–VCH, New York, Weinheim (1997); (b) J. K. Myers, E. N. Jacobsen, *J. Am. Chem. Soc.* **1999**, *121*, 8959–8960.
51 (a) T. E. Horstmann, D. J. Guerin, S. J. Miller, *Angew. Chem.* **2000**, *112*, 3781–3784; *Angew. Chem. Int. Ed.*

2000, 39, 3635–3638. (b) D. J. Guerin, S. J. Miller, J. Am. Chem. Soc. 2002, 124, 2134–2136.
52 See e.g.: H. L. van Lingen, W. Zhuang, T. Hansen, F. P. J. T. Rutjes, K. A. Jørgensen, Org. Biomol. Chem. 2003, 1, 1953–1958.
53 (a) R. Helder, R. Arends, W. Bolt, H. Hiemstra, H. Wynberg, Tetrahedron Lett. 1977, 25, 2181–2182; (b) H. Hiemstra, H. Wynberg, J. Am. Chem. Soc. 1981, 103, 417–430.
54 (a) T. Mukaiyama, A. Ikegawa, K. Suzuki, Chem. Lett. 1981, 165–168; (b) T. Mukaiyama, Tetrahedron 1981, 37, 4111–4119; (c) K. Suzuki, A. Ikegawa, T. Mukaiyama, Bull. Chem. Soc. Jpn. 1982, 55, 3277–3282.
55 (a) M. Asaoka, K. Shima, H. Takei, Tetrahedron Lett. 1987, 28, 5669–5672; (b) S. Colonna, R. Re, H. Wynberg, J. Chem. Soc., Perkin Trans 1 1981, 547–552; (c) A. Ito, K. Konishi, T. Aida, Tetrahedron Lett. 1996, 37, 2585–2588.
56 (a) H. Pracejus, F.-W. Wilcke, K. Hanemann, J. Prakt. Chem. 1977, 319, 219–229; (b) H. Yamashita, T. Mukaiyama, Chem. Lett. 1985, 363–366; (c) M. Shibasaki, A. Nishida, S. Ikegami, J. Chem. Soc., Chem. Commun. 1982, 1324–1325.
57 (a) N. Kobayashi, K. Iwai, J. Org. Chem. 1981, 46, 1823–1828; (b) J. Gawronski, K. Gawronska, H. Wynberg, J. Chem. Soc., Chem. Commun. 1981, 307–308; (c) J. K. Gawróński, K. Gawrónska, H. Kolbon, H. Wynberg, Recl. Trav. Chim. Pays-Bas 1983, 102, 479–483; (d) N. Kobayashi, K. Iwai, Tetrahedron Lett. 1980, 2167–2170; (e) P. Hodge, E. Khoshdel, L. Waterhouse, J. Chem. Soc., Perkin Trans. 1 1985, 2327–2331; (f) T. Danelli, R. Annunziata, M. Benaglia, M. Cinquini, F. Cozzi, G. Tocco, Tetrahedron: Asymmetry 2003, 14, 461–467.
58 A. Sera, K. Takagi, H. Katayama, H. Yamada, J. Org. Chem. 1988, 53, 1157–1161.
59 P. McDaid, Y. Chen, L. Deng, Angew. Chem. 2002, 114, 348–350; Angew. Chem. Int. Ed. 2002, 41, 338–340.
60 H. Wynberg, H. Pluim, Tetrahedron Lett. 1979, 1251–1254.
61 (a) W. ten Hoeve, H. Wynberg, J. Org. Chem. 1979, 44, 1508–1514; (b) For a proline-catalyzed hetero-domino Knoevenagel–Diels–Alder-epimerization sequence providing similar spiranes, see: D. B. Ramachary, N. S. Chowdari, C. F. Barbas III, Synlett 2003, 1910–1914.
62 B. M. Trost, C. D. Shuey, F. DiNinno jr., S. S. McElvain, J. Am. Chem. Soc. 1979, 101, 1284–1285.
63 Y. Hirai, T. Terada, T. Yamazaki, T. Momose, J. Chem. Soc., Perkin Trans. 1 1992, 509–516.
64 T. Ishikawa, Y. Oku, T. Tanaka, T. Kumamoto, Tetrahedron Lett. 1999, 40, 3777–3780.
65 T. Tanaka, T. Kumamoto, T. Ishikawa, Tetrahedron: Asymmetry 2000, 11, 4633–4637.
66 A. Merschaert, P. Delbeke, D. Daloze, G. Dive, Tetrahedron Lett. 2004, 45, 4697–4701.
67 A. Berkessel, Curr. Opinion Chem. Biol. 2003, 7, 409–419.

5
Nucleophilic Addition to C=N Double Bonds

5.1
Hydrocyanation of Imines (Strecker Reaction)

The Strecker reaction [1] starting from an aldehyde, ammonia, and a cyanide source is an efficient method for the preparation of α-amino acids. A popular version for asymmetric purposes is based on the use of preformed imines **1** and a subsequent nucleophilic addition of HCN or TMSCN in the presence of a chiral catalyst [2]. Besides asymmetric cyanations catalyzed by metal-complexes [3], several methods based on the use of organocatalysts have been developed [4–14]. The general organocatalytic asymmetric hydrocyanation reaction for the synthesis of α-amino nitriles **2** is shown in Scheme 5.1.



Scheme 5.1

Interestingly, completely different types of organocatalyst have been found to have catalytic hydrocyanation properties. Among these molecules are chiral diketopiperazine [4, 5], a bicyclic guanidine [6], and imine-containing urea and thiourea derivatives [7–13]. All these molecules contain an imino bond which seems to be beneficial for catalyzing the hydrocyanation process. Chiral *N*-oxides also promote the cyanosilylation of aldimines, although stoichiometric amounts of the oxides are required [14].

5.1.1
Chiral Diketopiperazines as Catalysts

The first catalytic asymmetric Strecker reaction was reported by the Lipton group using the cyclic dipeptide **5** as an organocatalyst [4, 5, 15]. This diketopiperazine **5** was prepared starting from (*S*)-phenylalanine and (*S*)-α-amino-γ-guanidinobutyric

Asymmetric Organocatalysis. Albrecht Berkessel and Harald Gröger
Copyright © 2005 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim
ISBN: 3-527-30517-3

acid. The presence of the basic guanidine side-chain was found to be a prerequisite for asymmetric induction. It is worthy of note that replacing the guanidine moiety by an imidazole moiety led to a non-enantioselective reaction (although the latter catalytic system had previously been shown to be suitable for enantioselective preparation of optically active cyanohydrins – see Section 6.1 and Ref. [16]).

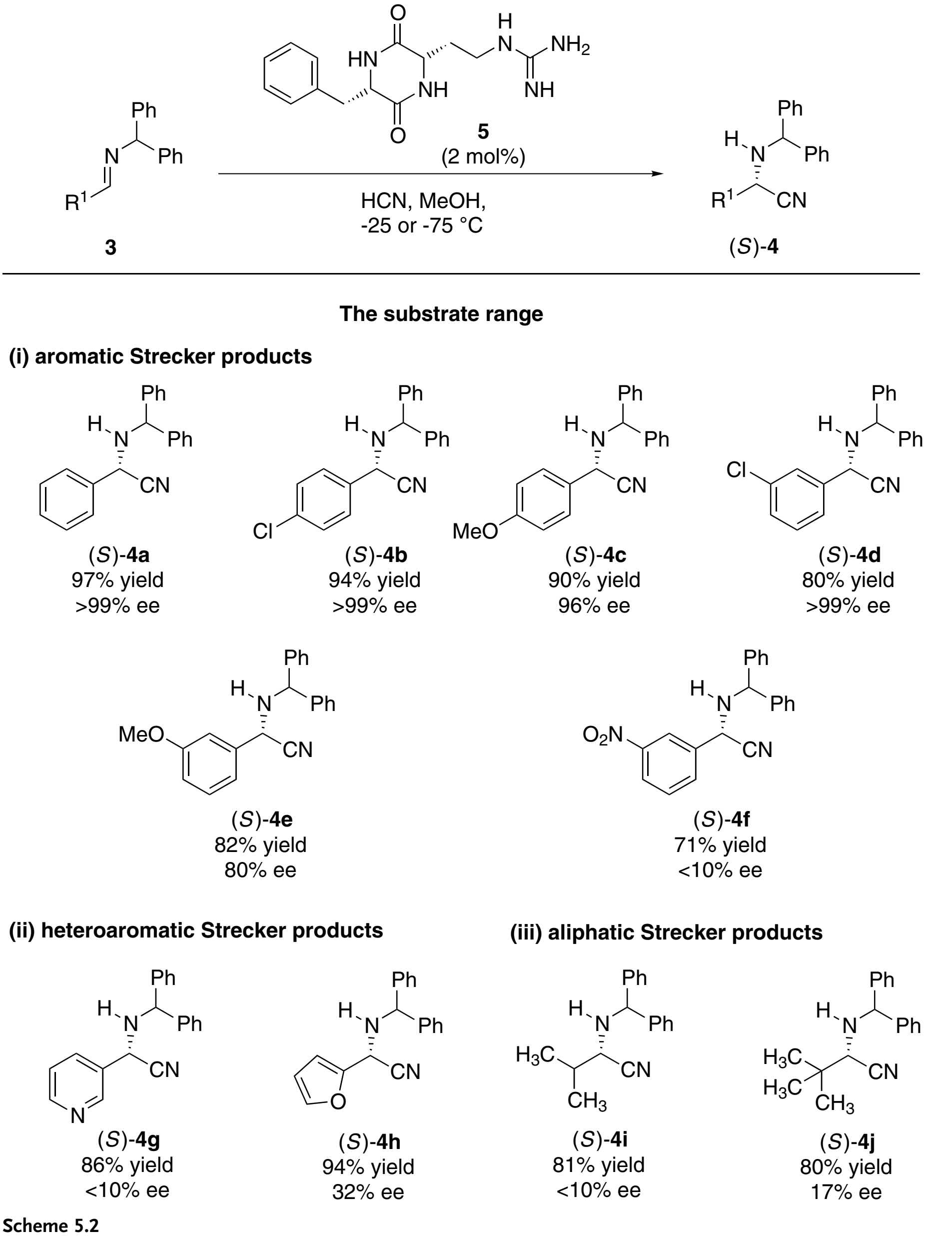
The reaction is performed with small amounts of catalyst – 2 mol% only [4]-, and a broad variety of *N*-substituted imines were found to be suitable as a substrate. Good to excellent enantioselectivity, in the range 80–99% ee, was usually obtained when using imines derived from benzaldehyde or electron-deficient aldehydes, although there are some exceptions. Scheme 5.2 shows the substrate range of this asymmetric diketopiperazine-catalyzed hydrocyanation developed by the Lipton group. For example, the amino nitrile (*S*)-**4a** was formed in high (97%) yield and with an excellent enantioselectivity (> 99% ee). In contrast, heteroatom-substituted aromatic imines resulted in substantially lower enantioselectivity. For example, enantioselectivity of 32% ee and <10% ee was obtained on starting from 2-furyl- and 3-pyridyl-containing imines, respectively. The organocatalyst **5** does not seem to be suitable for hydrocyanations of imines derived from alkyl-substituted aldehydes. For example, poor enantioselectivity of 17% ee or less was obtained for the amino nitriles (*S*)-**4i**, and (*S*)-**4j**.

The catalytic properties of the dipeptide were very sensitive to conditions such as solvent viscosity, enantioselective autocatalysis, and the method of crystallization of the catalyst. The last of these is particularly surprising, because **5** does not act as a heterogeneous catalyst but is soluble under the reaction conditions.

It should be added that attempts to perform a *direct* Strecker reaction starting from benzaldehyde, ammonia, and hydrocyanide in the presence of the organocatalyst **5** were also made by the Lipton group [4]. The resulting amino nitrile, however, was found to be racemic [4].

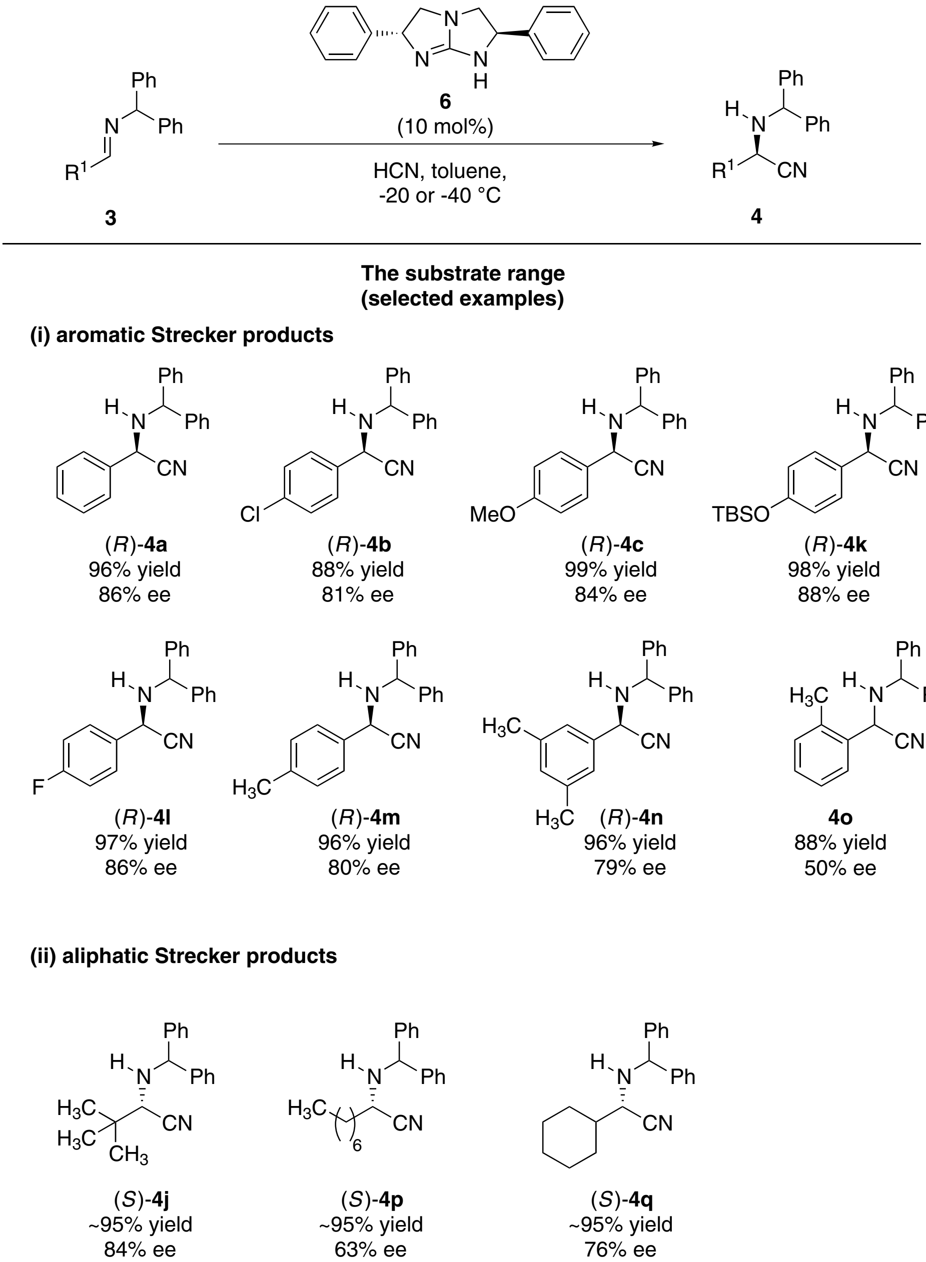
5.1.2
Chiral Guanidines as Catalysts

The Corey group developed an efficient asymmetric Strecker reaction based on use of catalytic amounts of the C_2-symmetric guanidine **6** [6]. The organocatalyst **6** is a completely different type of guanidine in which the guanidine functionality is embedded in a bicyclic framework [6]. In the presence of this catalyst high enantioselectivity was obtained when imines bearing an *N*-benzhydryl substituent were used as substrate. The choice of the *N*-substituent is important, because – in contrast – *N*-benzyl or *N*-(9-fluorenyl)-substituted imine substrates gave low enantioselectivity (0–25% ee). The hydrocyanation is typically performed with a catalytic amount of 10 mol% of **6** and has been shown to be general for a broad range of substituted aromatic imines. Enantioselectivity was in the range 80–88% ee for *p*-substituted benzaldimines whereas the *o*-substituted methylbenzaldimine and 1-naphthylaldimine gave somewhat lower enantioselectivity (50% ee and 70% ee, respectively). Compared with the diketopiperazine-catalyzed hydrocyanation described above,

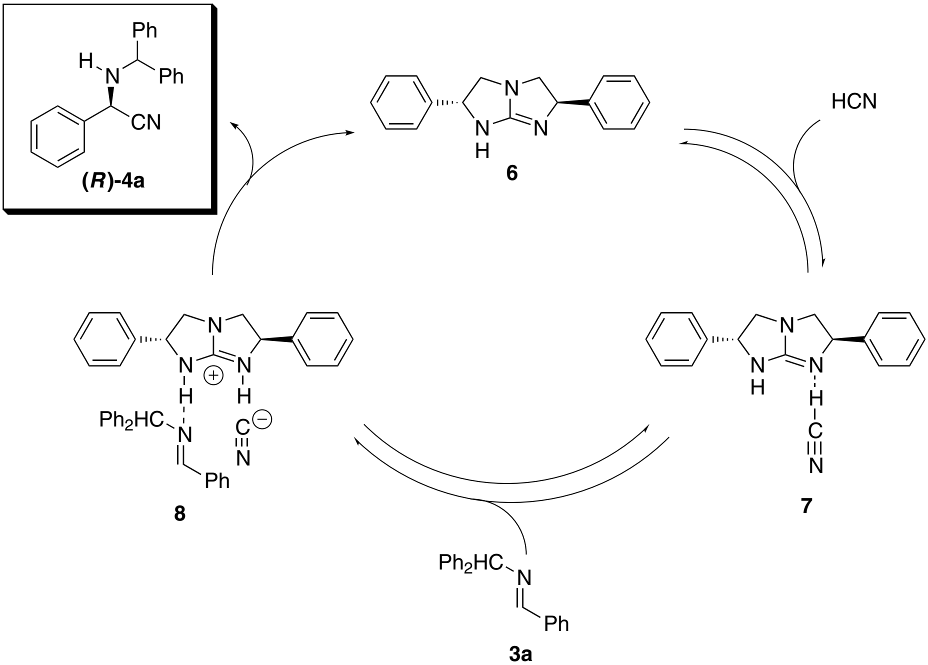


Scheme 5.2

aromatic substrates led to slightly lower enantioselectivity. It is, however, worthy of note that, in contrast with the diketopiperazine-catalyzed hydrocyanation, use of aliphatic aldimines as substrates led to good results with high yields (ca. 95%) and enantioselectivity in the range 63–84% ee (Scheme 5.3).


6
(10 mol%)
HCN, toluene,
-20 or -40 °C
3
4
The substrate range
(selected examples)
(i) aromatic Strecker products
(R)-4a
96% yield
86% ee
(R)-4b
88% yield
81% ee
(R)-4c
99% yield
84% ee
(R)-4k
98% yield
88% ee
(R)-4l
97% yield
86% ee
(R)-4m
96% yield
80% ee
(R)-4n
96% yield
79% ee
4o
88% yield
50% ee
(ii) aliphatic Strecker products
(S)-4j
~95% yield
84% ee
(S)-4p
~95% yield
63% ee
(S)-4q
~95% yield
76% ee

Scheme 5.3



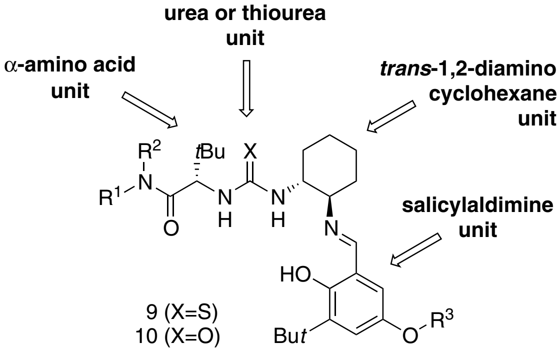
Scheme 5.4

The catalyst **6** can be recovered for re-use in 80–90% yield by extraction with oxalic acid. The α-amino nitrile products were easily transformed into the corresponding α-amino acids by removing the benzhydryl group by hydrolysis in HCl.

The reaction mechanism proposed by the Corey group is shown in Scheme 5.4 [6]. The initial step is the formation of a guanidinium cyanide complex, **7**; this is followed by generation of complex **8**. In this complex **8** both components (imine and cyanide) are attached to the organocatalyst by hydrogen bonds [6]. In this context, an interesting experimental result is that the *N*-methylated catalyst is inactive. This indicates the mechanistic importance of the hydrogen atom (attached to the nitrogen) in binding the nitrogen of the imine bond in the transition state. Subsequent steps are the formation and release of the optically active α-amino nitrile (*R*)-**4a**. The Corey group also modeled transition state assemblies and thereby explained the opposite configurations obtained for aromatic and aliphatic α-amino nitrile products **4** [6].

5.1.3
Chiral Ureas and Thioureas as Catalysts

A very efficient method for hydrocyanation of aldimines and ketimines has been developed by the Jacobsen group. Chiral urea or thiourea derivatives containing an imine bond of type **9** and **10** were used as organocatalysts [7–13]. The core



Scheme 5.5

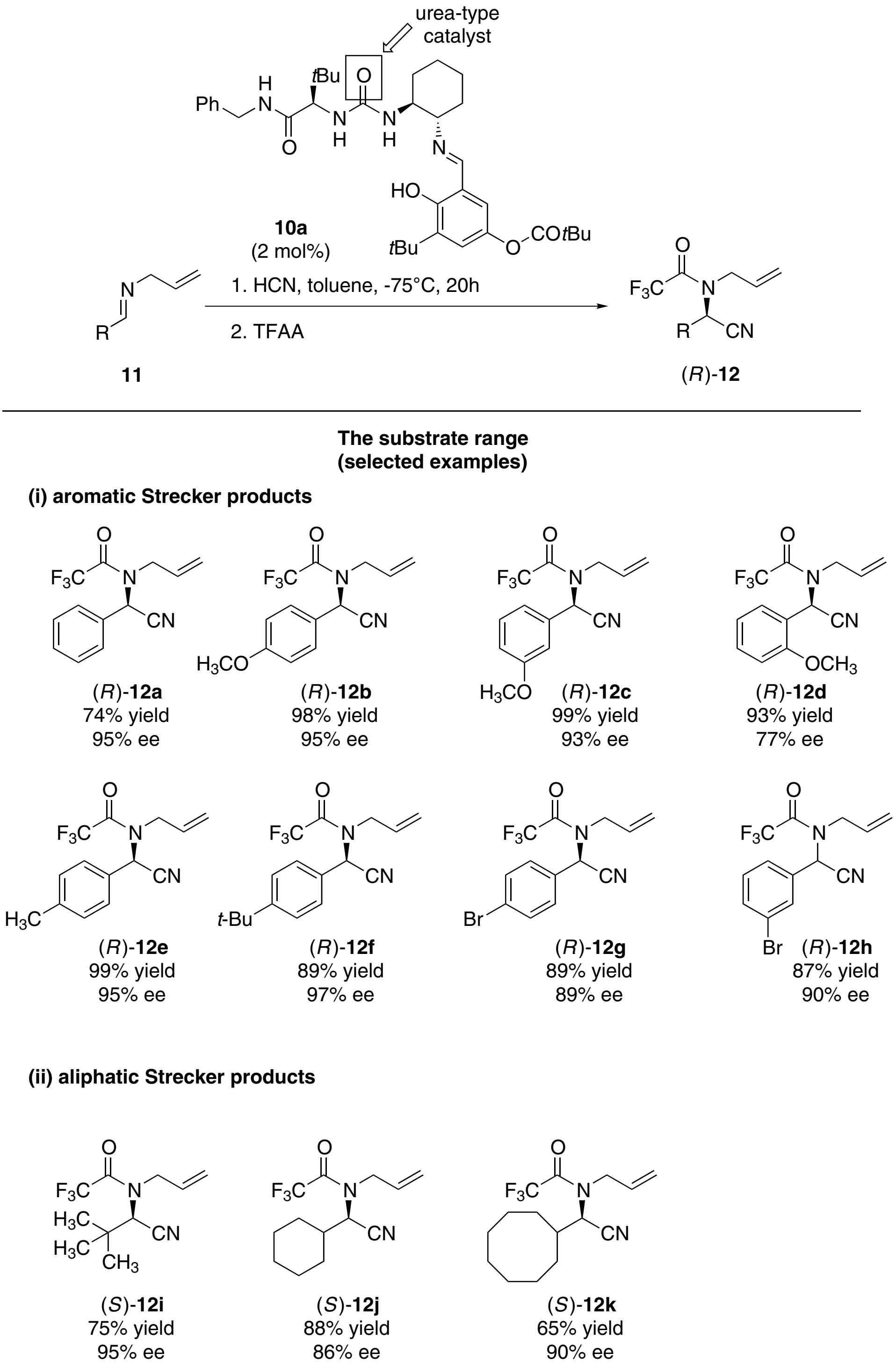
structure and typical structural parts of these types of organocatalyst are shown in Scheme 5.5. Besides the urea or thiourea unit these organocatalysts contain a substituted salicylaldimine and enantiomerically pure 1,2-cyclohexyldiamine units. An optically active alkyl α-amino acid, preferably L-*tert*-leucine, is also integrated in these catalysts.

This new type of organocatalyst was found by parallel screening [7]. Investigation of numerous variants of Schiff base organocatalysts led to an optimized catalyst of type **9** bearing substituents on the salicylaldimine unit and thiourea functionality. In the presence of 2 mol% of such a catalyst of type **9** asymmetric hydrocyanation gave the α-amino nitrile (*R*)-**12a** in 78% yield and with 91% ee [7]. Detailed investigation of scope and limitations was performed with the further optimized soluble urea catalyst, **10a** [10]. In the presence of 2 mol% **10a** yields of up to 74 to 99% and enantioselectivity of 77 to 97% ee were obtained for the corresponding aromatic α-amino nitriles, e.g., (*R*)-**12a–h** (Scheme 5.6) [10]. For example, a yield of 74% and improved enantioselectivity of 95% ee were observed for the product (*R*)-**12a**. Higher yields (at least 87%) and excellent enantioselectivity also were obtained for substituted *N*-allyl benzaldimines (*R*)-**12b**–**12h**.

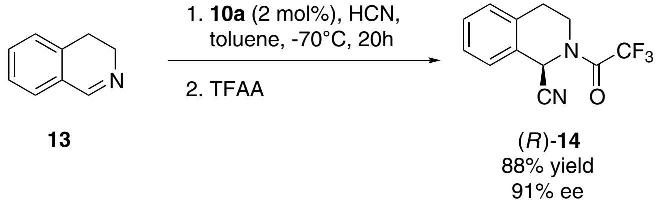
In addition, acyclic aliphatic *N*-allyl imines and cycloalkylimines were acceptable starting materials for the asymmetric hydrocyanation and enantioselectivity of up to 95% ee was obtained by use of **10a** as catalyst [10]. Representative examples of the range of substrates are summarized in Scheme 5.6. It should be added that as an alternative to the *N*-allyl imines the analogous *N*-benzyl imines can be efficiently used as starting material [10]. An optimized procedure for preparation of the catalyst **10a** has recently been reported by the Jacobsen group [11].

Jacobsen et al. have also demonstrated the usefulness of this method for asymmetric hydrocyanation of cyclic imines [10]. An example is the efficient synthesis of (*R*)-**14** in 88% yield and with 91% ee (Scheme 5.7). Thus, in addition to the hydrocyanation of acyclic imines which are mainly *E*-isomers, *Z*-imines can also be used efficiently.

The Jacobsen group also achieved process improvement with respect to catalyst immobilizaion and recycling [10]. In this recycling study a polymer-supported


urea-type catalyst
10a
(2 mol%)
1. HCN, toluene, -75°C, 20h
2. TFAA
11
(R)-12
The substrate range
(selected examples)
(i) aromatic Strecker products
(R)-12a
74% yield
95% ee
(R)-12b
98% yield
95% ee
(R)-12c
99% yield
93% ee
(R)-12d
93% yield
77% ee
(R)-12e
99% yield
95% ee
(R)-12f
89% yield
97% ee
(R)-12g
89% yield
89% ee
(R)-12h
87% yield
90% ee
(ii) aliphatic Strecker products
(S)-12i
75% yield
95% ee
(S)-12j
88% yield
86% ee
(S)-12k
65% yield
90% ee

Scheme 5.6



Scheme 5.7

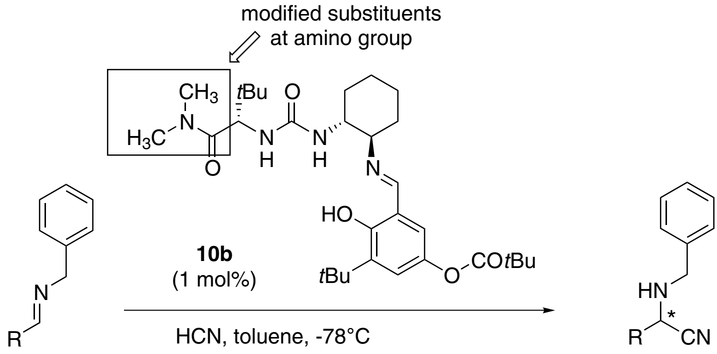
catalyst of type **9** has been re-used very efficiently, maintaining both high yields (96–98%) and enantioselectivity (92–93% ee) over (at least) ten reaction cycles [10]. A specific advantage is the easy separation of this immobilized catalyst from the reaction mixture.

It should be added that Jacobsen-type hydrocyanation has already been commercially applied for production of optically active α-amino acids at Chirex (see also Chapter 14).

Very recently further optimization was achieved on the basis of rational "mechanism-driven" optimization (for this mechanistic study [12], see the corresponding section below). The resulting, further improved catalyst **10b** was found to be superior to **9** and **10a**, and is the most enantioselective Strecker catalyst yet prepared [12]. Starting from both aliphatic and aromatic aldimines, excellent enantioselectivity in the range 96–99.3% ee was obtained even in the presence of only 1 mol% **10b**. An overview of the excellent enantioselectivity obtained with **10b**, and comparison with ee values obtained in the presence of catalyst **10a**, are given in Scheme 5.8.

The Jacobsen group successfully extended the range of application of these organocatalysts to the first highly enantioselective hydrocyanation of ketimines [13]. This reaction gives α-amino nitriles, e.g. of type **18**, bearing a stereogenic quaternary carbon center, which are suitable precursors for synthesis of α,α-disubstituted α-amino acids. The optimized reaction system consists of the soluble catalyst **10a** (2 mol%) in combination with *N*-benzyl-substituted ketimines. Study of the substrate range revealed enantioselectivity was usually high with 88–95% ee for a broad variety of *N*-benzylated aromatic substrates **17** (Scheme 5.9) [13]. For example, the amino nitrile (*R*)-**19a** was obtained in 97% yield and with 90% ee. *O*-Substituted ketimines, however, are not good substrates. This is exemplified by the synthesis of (*R*)-**18h** in 45% yield and 42% ee only. Aliphatic imines also can serve as good substrates. For example, use of *N*-benzyl *tert*-butylmethylimine, **17i**, as a selected aliphatic imine led to (*R*)-**18i** in 98% yield and with 70% ee. Some of the samples of (*R*)-**18** were obtained in the crystalline form, so that further enhancement of enantiopurity by recrystallization was possible and led to enantiomerically pure products with impressive >99.9% ee and 75–79% overall isolated yields (e.g. for (*R*)-**18c**, and (*R*)-**18e**,**f**). On the basis of the α-amino nitriles (*R*)-**18**, attractive access to quaternary α-amino acids was realized after subsequent formylation and hydrolysis of the α-amino nitriles.

A very detailed structural and mechanistic study of this method has also been



15

16

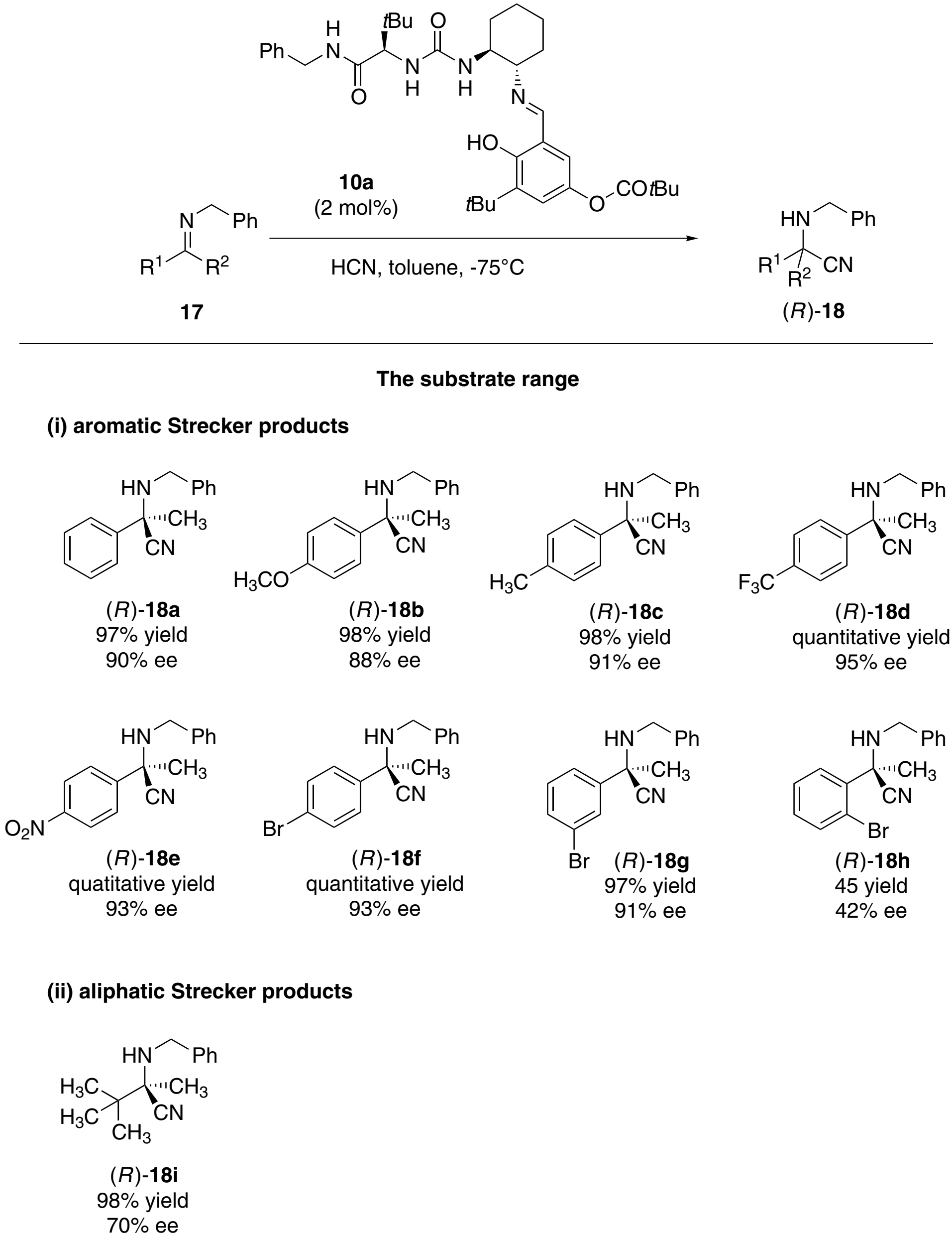
R	ee [%]
Ph	99.3 (96)
i-Pr	97 (80)
t-Bu	99.3 (96)
n-Pent	96 (79)

a) For comparison, in parentheses the ee values obtained in the presence of catalyst **10a** are given.

Scheme 5.8

conducted by the Jacobsen group [12]. This study showed that the Schiff base catalyst **10a** has a well-defined secondary structure in solution. The hydrocyanation reaction proceeds according to a Michaelis–Menten kinetic model with first order dependence on **10a** and HCN and saturation kinetics with regard to the imine substrate. Reversible formation of a complex between **10a** and the imine, by hydrogen bonding, was therefore postulated [12]. The two urea hydrogen atoms in **10a** have been identified as the relevant protons involved in this hydrogen bond formation. In addition, the Strecker reactions involve binding of the imine as the *Z* isomer.

A 3D-structure of the substrate–catalyst complex, which was supported by molecular modeling, revealed that the large group of the imine is directed away from the catalyst. This complex of the catalyst with the *Z* imine, and a solution structure of the organocatalyst, are shown in Figure 5.1 [12]. This explains the broad substrate tolerance which is independent of steric or electronic properties. A further important hypothesis is that addition of HCN occurs over the diaminocyclohexane framework in **10a**; this led to the prediction that a more bulky amino acid/amide portion should give a further improved catalyst. This conclusion led to (model-driven) optimization which resulted in the improved and highly enantioselective Strecker catalyst **10b** (for preparative results with this catalyst see Scheme 5.8 and related text) [12].


10a
(2 mol%)
HCN, toluene, -75°C
17
(R)-18
The substrate range
(i) aromatic Strecker products
(R)-18a
97% yield
90% ee
(R)-18b
98% yield
88% ee
(R)-18c
98% yield
91% ee
(R)-18d
quantitative yield
95% ee
(R)-18e
quatitative yield
93% ee
(R)-18f
quantitative yield
93% ee
(R)-18g
97% yield
91% ee
(R)-18h
45 yield
42% ee
(ii) aliphatic Strecker products
(R)-18i
98% yield
70% ee

Scheme 5.9

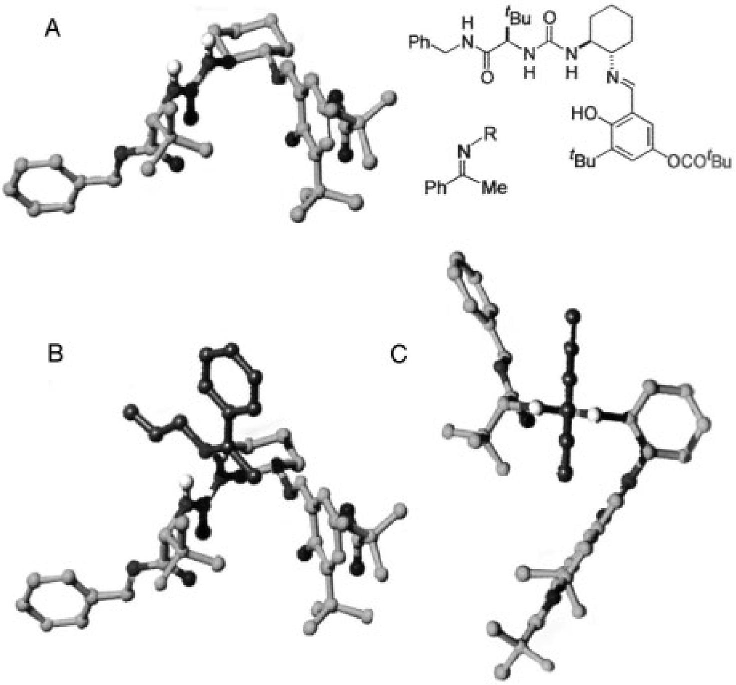
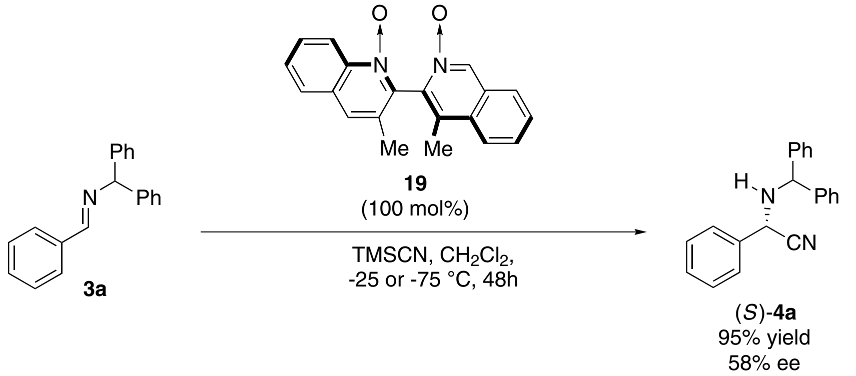


Fig. 5.1. (A) Solution structure of catalyst **10a** and (B, C) two views of the complex generated on binding of a *Z* imine, as determined by NMR spectroscopy. (From Ref. [12] with permission from the ACS.)

5.1.4
Chiral *N*-Oxides as "Catalysts"

The Feng group showed that organic molecules without an imine bond also seem to be able to catalyze the cyanation of imines [14]. In the presence of (stoichiometric) amount of a chiral *N*-oxide, **19**, addition of trimethylsilylcyanide to several types of aldimine gave the desired α-amino nitriles with enantioselectivity up to 73% ee [14]. For example, (*S*)-**4a** is obtained in 95% yield and with 58% ee (Scheme 5.10). In addition to medium enantioselectivity, a drawback of this method is the need for stoichiometric amounts of the chiral *N*-oxide. The use of trimethylsilylcyanide is also less recommendable than HCN from both atom-economical and industrial considerations.

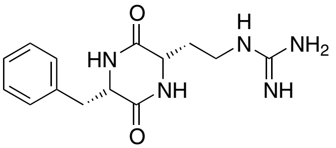
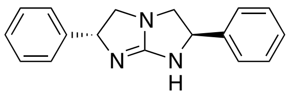
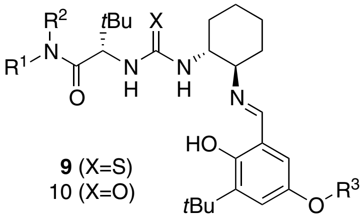
In conclusion, great achievements have recently been made in organocatalytic asymmetric hydrocyanation of imines. The organocatalysts developed are highly efficient with regard to both yield and enantioselectivity. The variety of catalysts also indicates high potential for future work. The current situation is a good starting point for new applications in the field of α-amino nitriles and derivatives thereof (in particular α-amino acids). Among future challenges is the development of *direct*



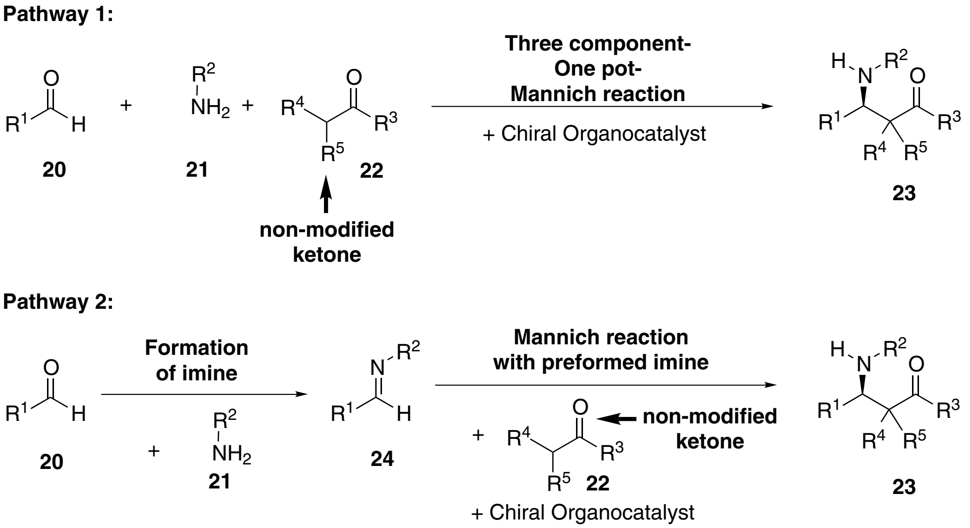
Scheme 5.10

access to the Strecker products starting from aldehyde, amine, and hydrogen cyanide [17]. Thus, isolation of the preformed imine could be avoided leading directly to the desired α-amino nitriles and acids in a three-component, one-pot reaction.

A graphical summary of the developed organocatalytic hydrocyanation methods and comparison of their main key features are given in Scheme 5.11.

Catalyst structure	Substrate range	Catalytic amount	Range of yield [%]	Range of ee [%]
 5	aromatic aldimines (not NO_2- subst. and heteroatoms)	2 mol%	82-97	80-99
 6	aromatic, aliphatic aldimines	10 mol%	80-99	50-88
 **9** (X=S) 10 (X=O)	aromatic, aliphatic aldimines and ketimines	1-2 mol%	65-98 45-100	77-99 42-95

Scheme 5.11



Scheme 5.12

5.2 The Mannich Reaction

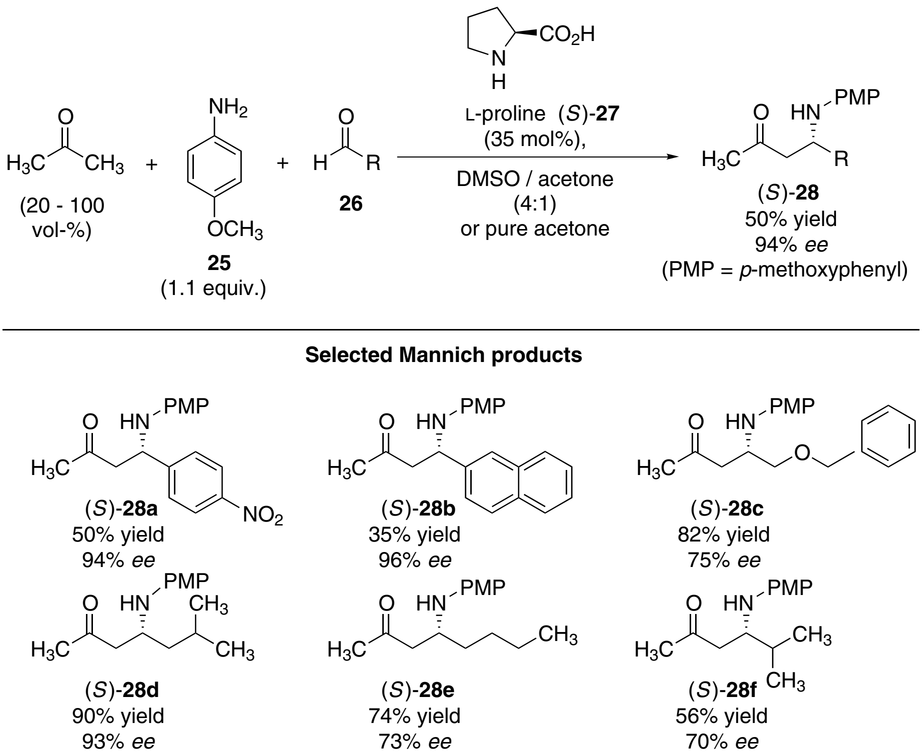
The Mannich reaction [18, 19] is a widely applied means of producing *β*-amino carbonyl compounds starting from cheap and readily available substrates. In this reaction an aldehyde **20**, an amine **21**, and a ketone **22** react in a three-component–one-pot synthesis (Scheme 5.12, pathway 1). As a synthetic alternative, the reaction can also be performed as a nucleophilic addition of a C-nucleophile **22** to a preformed imine **24** which is prepared starting from the aldehyde and an amine source (Scheme 5.12, pathway 2).

An asymmetric Mannich reaction was recently successfully achieved by means of different types of catalyst, metal- and organocatalysts [20, 21]. With the latter the reaction can be performed asymmetrically by use of L-proline and related compounds as chiral organocatalyst [22–35]. A key advantage of the proline-catalyzed route is that unmodified ketones are used as donors, which is synthetically highly attractive. In contrast, many other asymmetric catalytic methods require preformed enolate equivalents as nucleophile.

In addition, chiral Schiff base catalysts, which were developed previously for the Strecker reaction, were also found to be suitable catalysts for the Mannich reaction starting from imines and enolates [36, 37]. Very recently, further efficient organocatalysts for the Mannich reaction, such as chiral pyrrolidinyltetrazole and chiral binaphthyl phosphoric acids, have been reported [38].

5.2.1 Enantioselective Direct Mannich Reaction: Products with One Stereogenic Center

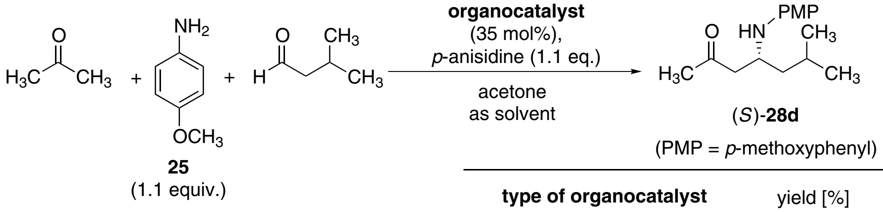
Optically active *β*-amino ketones (*S*)-**28** with one stereogenic center can be efficiently prepared in the presence of 35 mol% L-proline (*S*)-**27** with acetone as a



Scheme 5.13

ketone nucleophile [22]. The corresponding three-component Mannich reactions, developed by List et al., furnished the *β*-amino ketones (*S*)-**28** with enantioselectivity in the range 70 to 96% ee (Scheme 5.13). The yields varied substantially, from 35 to 90%, depending on the type of substrate. This catalytic method [22–24] was applied to a series of different aromatic and aliphatic aldehydes. The best enantioselectivity was achieved with aromatic substrates, resulting in the formation of the corresponding products (*S*)-**28a**, and (*S*)-**28b** with 94% ee and 96% ee, respectively. With aliphatic substrates enantioselectivity varied substantially. High ee can, however, also be achieved for those substrates, as shown for the product (*S*)-**28d** with 93% ee.

The right choice of amine plays an important role in the synthetic utility of this organocatalytic Mannich reaction. For synthesis of Mannich products bearing a primary amino group the use of amines with readily removable nitrogen substituents is desirable. A preferred amine, *p*-anisidine **25** was found to form PMP-protected *β*-amino ketones **28** in the Mannich reaction. This PMP protecting group has the advantage that it can be easily removed under oxidative conditions in a subsequent transformation [22, 23]. Other aniline derivatives have been also studied but



type of organocatalyst	yield [%]	ee [%]
(S)-27	90	93
(S)-29	56	76
(S)-30	22	15
(S)-31 (DMTC)	60	16
(S)-32	26	0

Scheme 5.14

were found to afford less satisfactory yields and enantioselectivity [23]. Thus, the discovery of other suitable amine components, leading to (more) easily removable protecting groups would be desirable to broaden the applicability of this challenging proline-catalyzed Mannich reaction.

Very recently, the List group applied this proline-catalyzed Mannich reaction efficiently in multi-step syntheses of several α-amino acid derivatives, such as protected 1,2-amino alcohol derivatives and oxazolidin-2-ones [25].

Under the reaction conditions used in the one-pot Mannich reaction described above, L-proline (*S*)-**27** was clearly found to be the preferred organocatalyst. As is apparent from Scheme 5.14, the best yield (90%) and enantioselectivity (93% ee) were obtained by use of this organocatalyst [23]. The suitability of all other organocatalysts used in this one-pot reaction, using 3-methylbutanal as aldehyde, was poor. Remarkably lower yields and poor enantioselectivity were obtained when the thiazolidine catalyst (*S*)-**31** and other pyrrolidine-based organocatalysts were used.

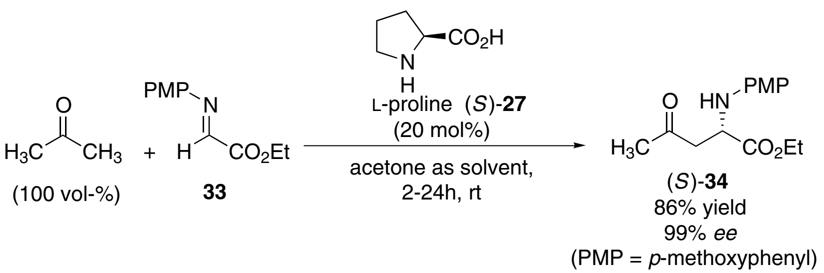
Interestingly, however, another comparative study [24] revealed the capacity of other amines related to L-proline (*S*)-**27** to function as organocatalysts in the Mannich reaction under modified reaction conditions [24]. As shown for a model reaction using preformed imines derived from *o*-anisidine, the thiazolidine carboxylic

acid (*S*)-**31** and a protonated salt of the diamine (*S*)-**32**, had comparable catalytic properties [24]. Nevertheless, so far it seems that in general L-proline is superior to those other organocatalysts for the asymmetric Mannich reaction.

Mechanistically it seems that the reactions follow an enamine mechanism, in which the enamine derived from the ketone and proline reacts with the imine formed *in situ* from the aldehyde and *p*-anisidine.

An interesting extension of this Mannich reaction was reported very recently by the Barbas group [26]. An α-imino glyoxylate **33** was used as a (preformed imine) starting material. The corresponding Mannich reaction furnished directly functionalized α-amino acids of type (*S*)-**34** (see also the selected example in Scheme 5.15) which are difficult to synthesize by other synthetic routes.

In the presence of L-proline (20 mol%) as catalyst and acetone as a solvent (Scheme 5.15), the product (*S*)-**34** was isolated in 86% yield and with excellent enantioselectivity (99% ee). When the reaction was carried out in (4:1) DMSO/acetone solvent, yield and enantioselectivity decreased slightly (82% yield; 95% ee).

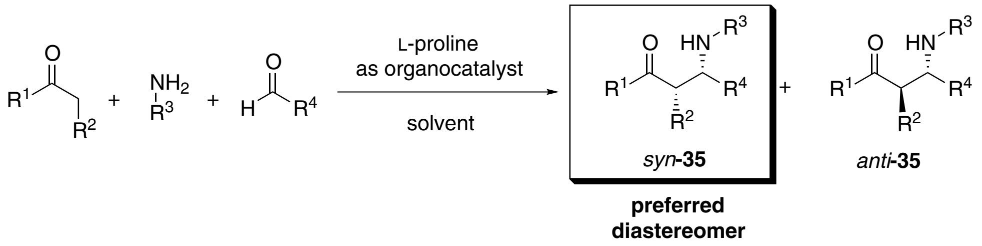


Scheme 5.15

5.2.2
Enantio- and Diastereoselective Direct Mannich Reaction: Products with Two Stereogenic Centers

It is worthy of note that – similarly to the proline catalyzed aldol reaction – the Mannich reaction can also be extended to an enantio- and diastereoselective process in which two stereogenic centers are formed in one step, although using non-chiral starting materials (Scheme 5.16) [22, 23, 26, 27, 28]. In these reactions substituted acetone or acetaldehyde derivatives, rather than acetone, serve as donor. In contrast with the anti diastereoselectivity observed for the aldol reaction (Section 6.2.1.2), the proline-catalyzed Mannich reaction furnishes products with syn diastereoselectivity [23]. A proline-derived catalyst, which led to the formation of anti Mannich products has, however, been found by the Barbas group [29].

The List group developed an efficient synthesis for syn Mannich products by using proline as a catalyst and ketone donors [23]. Starting from 2-butanone as

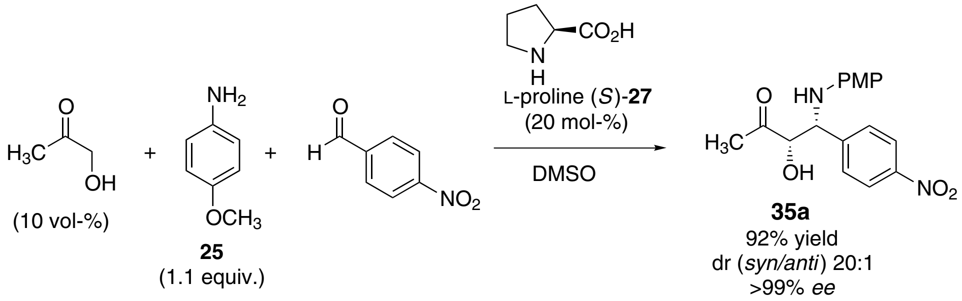


Scheme 5.16

donor and *p*-nitrobenzaldehyde as acceptor a 2.5:1 regioisomeric mixture was obtained (combined yield of regioisomers 96%) [23]. The enantioselectivity (up to 99%) and diastereoselectivity (d.r. > 39:1) were high. For other substituted acetone derivatives, for example methoxy- or hydroxyacetone, the formation of products resulting from the more substituted α-side of the ketone is favored with high regioselectivity, and the major regioisomer only was isolated and characterized [23].

Use of hydroxyacetone as donor in the asymmetric Mannich reaction led to the formation of optically active syn *β*-amino alcohols bearing two stereogenic centers [22, 23]. In the presence of 35 mol% L-proline as organocatalyst several types of syn *β*-amino alcohol *syn*-**35** were successfully synthesized with enantioselectivity up to 99% ee and high diastereomeric ratio. For example, a high yield of 92%, a diastereomeric ratio of 20:1, and enantioselectivity >99% ee were observed by List et al. for formation of the syn *β*-amino alcohol **35a** (Scheme 5.17) [23]. In addition to hydroxyacetone the methylated derivative methoxyacetone was also applied successfully in this reaction (93% yield, d.r. > 39:1, >99% ee).

The Mannich reaction using PMP-protected α-imino glyoxylate, **33**, can also be conducted enantio- and diastereoselectively when using substituted acetone derivatives, as has been successfully shown by the Barbas group [26–28]. Several types of ketone are accepted as donors in the presence of 20 mol% of L-proline as catalyst [26]. This type of Mannich reaction provides keto-functionalized syn α-amino acid

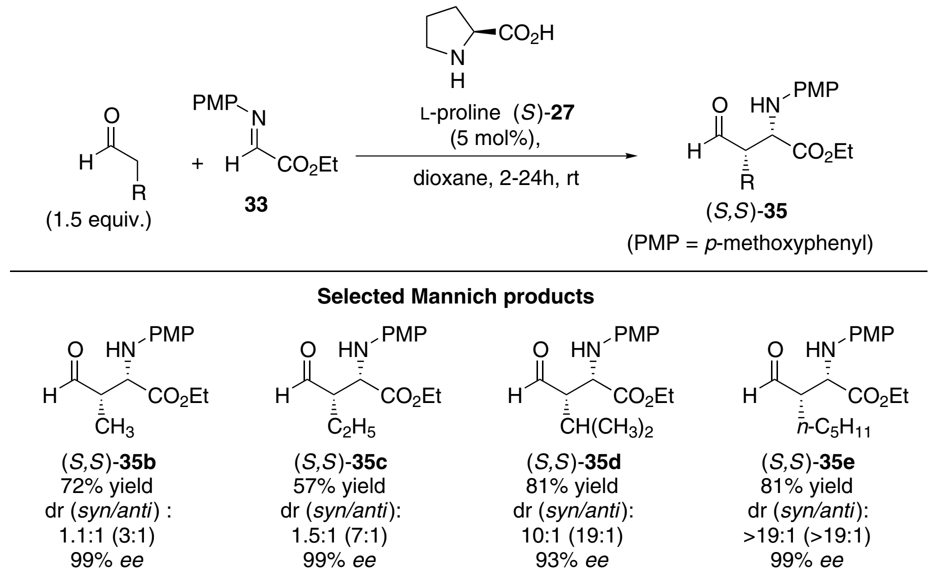


Scheme 5.17

esters in high yields and with excellent regio-, diastereo-, and enantioselectivity. In contrast with other methods leading to these target molecules, this approach uses achiral, readily available substrates which can be directly converted into the desired products in a one-pot reaction. Thus, this new method is an unusual but innovative and efficient way of producing non-natural optically active α-amino acids based on an inexpensive and environmental friendly catalyst.

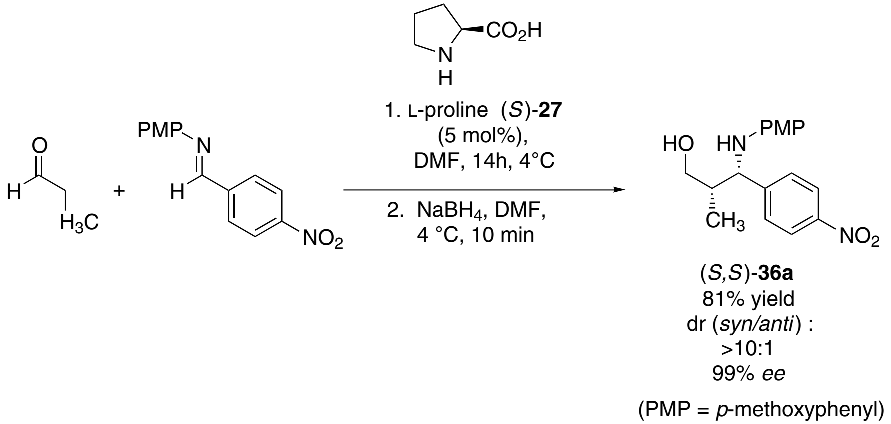
It is worthy of note that the choice of donor is not restricted to ketones. The Barbas group also successfully applied acetaldehyde and derivatives thereof as suitable donors (Scheme 5.18) [27, 28, 30]. This reaction is the first example of a catalytic asymmetric Mannich reaction using unmodified aldehydes. Under optimized reaction conditions the resulting products, e.g. **35b–e**, were obtained with excellent enantioselectivity in the range 93 to 99% ee (Scheme 5.18). The yields were in the range 57 to 89%. The diastereomeric ratio differs significantly, from 3:1 to >19:1, depending on the type of aldehyde donor. The optically active products are interesting intermediates for preparation of β-lactams and γ-amino alcohols bearing two stereogenic centers. During optimization of the reaction conditions it was found that in the presence of 1,4-dioxane as solvent the amount of catalyst could be reduced to 5 mol% [28]. Study of a broad range of proline derivatives to determine their catalytic potential revealed that proline, in particular, hydroxyproline, and its *tert*-butyl ether derivative are efficient [28].

The Barbas group also showed that aromatic aldimines are suitable substrates for



(dr values in parantheses are referring to those determined from the crude products)

Scheme 5.18



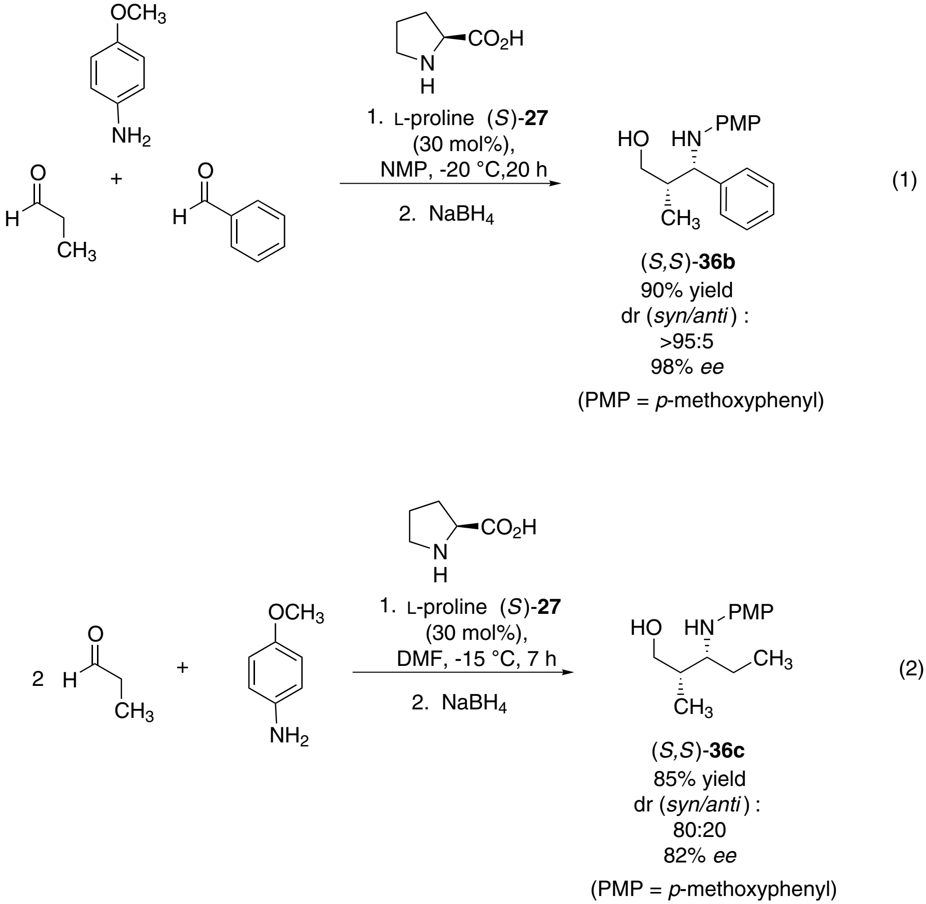
Scheme 5.19

the Mannich reaction with unmodified aldehydes [28]. This reaction also proceeds with formation of the desired products in good yields and with high diastereo- and enantioselectivity. A selected example is shown in Scheme 5.19. The addition of propanal to imine **35** gave the product *syn*-(*S*,*S*)-**36a** with a high diastereoselectivity and an excellent enantioselectivity (99% ee). This type of Mannich reaction tolerates amounts of water up to 10% (v/v) without loss of enantioselectivity [28].

Extension of this reaction toward a one-pot asymmetric Mannich-hydrocyanation reaction sequence was also reported by the Barbas group [29]. In this one-pot two-step process proline-catalyzed asymmetric Mannich reaction of unmodified aldehydes with the α-imino glyoxylate was performed first, then diastereoselective *in situ* cyanation. The resulting β-cyanohydroxymethyl α-amino acids were obtained with high enantioselectivity (93–99% ee) [29]. Another one-pot two-step reaction developed by Barbas et al. is the Mannich-allylation reaction in which the proline-catalyzed Mannich reaction is combined with an indium-promoted allylation [30]. This one-pot synthesis was conducted in aqueous media and is the first example of a direct organocatalytic Mannich reaction in aqueous media [28, 30].

The Barbas and Hayashi groups also independently showed that instead of using preformed imines, the imine can be formed *in situ* [28, 31, 32]. The resulting one-pot three-component Mannich reaction starting from aliphatic and an aromatic aldehyde and *p*-anisidine gave the desired syn Mannich products with high diastereoselectivity and excellent enantioselectivity (up to >99% ee) [28, 31, 32]. A selected example is shown in Scheme 5.20, Eq. (1) [31]. It is worthy of note that only minimal amounts of undesired cross-aldol products or self-Mannich products are formed. In the absence of a second (aromatic) aldehyde, however, aliphatic aldehydes undergo direct asymmetric self-Mannich reaction catalyzed by proline [28]. Making use of this modified one-pot Mannich reaction, several self-Mannich products were formed, usually with high enantioselectivity. A selected example is given in Scheme 5.20, Eq. (2) [28].

Development of a method for formation of the opposite diastereomers, i.e. anti

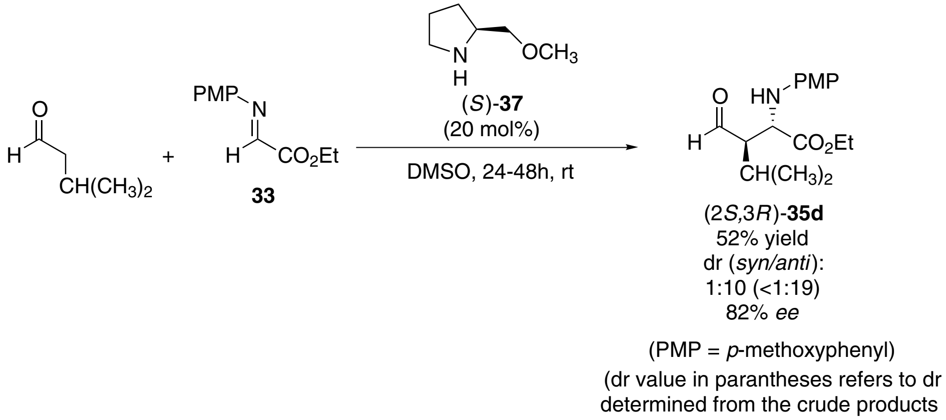


Scheme 5.20

Mannich products, has also been reported by the Barbas group [33]. Using the (*S*)-2-methoxymethylpyrrolidine (*S*)-**37** as catalyst in the addition of unmodified aldehydes to α-imino glyoxylate led to diastereo- and enantioselective formation of the anti products with d.r. (*syn*/*anti*) up to >19:1 and 92% ee [33]. A selected example is shown in Scheme 5.21.

5.2.3
Proline-catalyzed Mannich Reaction: Process Development and Optimization

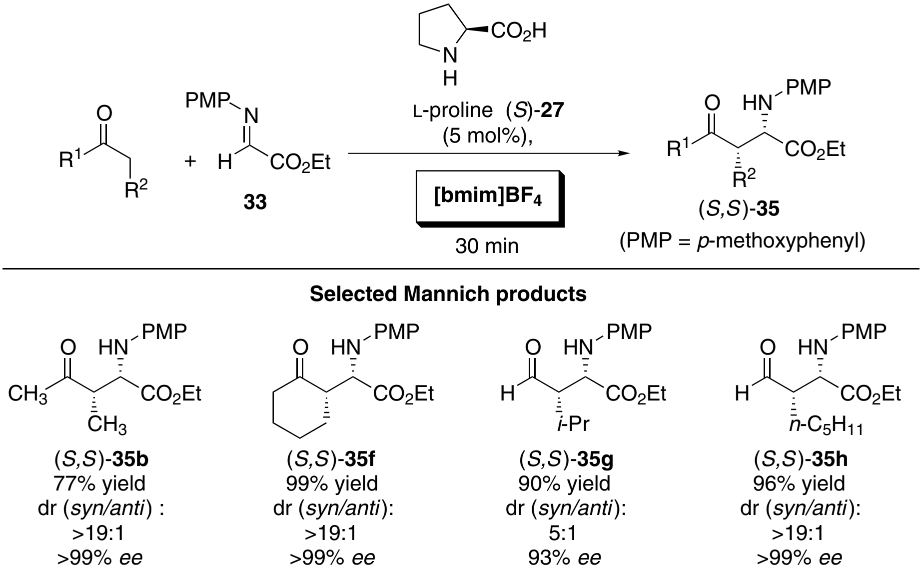
Despite their high synthetic potential, when L-proline-catalyzed reactions are evaluated, catalytic amounts in the range 20 to 35% and use of excess ketone (usually 20% *v*/*v*) represent reaction parameters to be optimized. Experimental studies addressing this issue have been conducted and impressive solutions were found by the List group [23]. As a model reaction the Mannich synthesis using *p*-nitro-



Scheme 5.21

benzaldehyde, *p*-anisidine, and hydroxyacetone in the presence of L-proline was chosen. It is worthy of note that the amount of L-proline can be efficiently reduced to 10 mol% while still achieving high yields ($>$ 90%) at reasonable reaction time ($<$ 5 h). It is also possible to reduce the amount of the ketone component to 1.3 equivalents without a significant loss of yield [23]. This result is important, because this type of organocatalytic Mannich reaction is now economically attractive even when use of more expensive ketones is required. A similar result has been obtained by the Barbas group for the proline-catalyzed Mannich reaction with unmodified aldehydes [28]. As described above, a small amount of catalyst could be used when 1,4-dioxane was employed as solvent.

Another interesting improvement of the process was reported by the Barbas group, who showed the beneficial effect of ionic liquids as reaction media [34, 39]. Starting from α-imino glyoxylate as imino component the proline-catalyzed Mannich reaction proceeds very efficiently in [bmim]BF_4 as ionic liquid [34]. Aldehydes and ketones can be used as nucleophiles. Besides high yields of 77–99%, excellent syn diastereo- and enantioselectivity were obtained for syn products of type **35** (Scheme 5.22). The diastereomeric ratio was in the range (syn/trans) = 5:1 to >19:1 and enantioselectivity was impressive with 93–99% ee [34]. In addition, the reaction time is very short – 30 min only. Thus, compared with traditional solvents the reaction rate increased by factor of 4–50 when the reaction is conducted in ionic liquids. The higher reaction rate might result from activation of the imine components by the ionic liquid. Further advantages of the use of ionic liquids are facile product isolation and recovery and re-use of the proline catalyst. Representative examples are shown in Scheme 5.22. Ionic liquids were also applied in the proline-catalyzed asymmetric three-component Mannich-reaction [34]. In this reaction yields and enantioselectivity were comparable with those obtained with traditional solvents. Once again, however, the reaction proceeded significantly more rapidly. Among the limitations of the use of ionic liquids are the remarkably lower diastereo- and enantioselectivity obtained when hydroxyacetone is used as donor



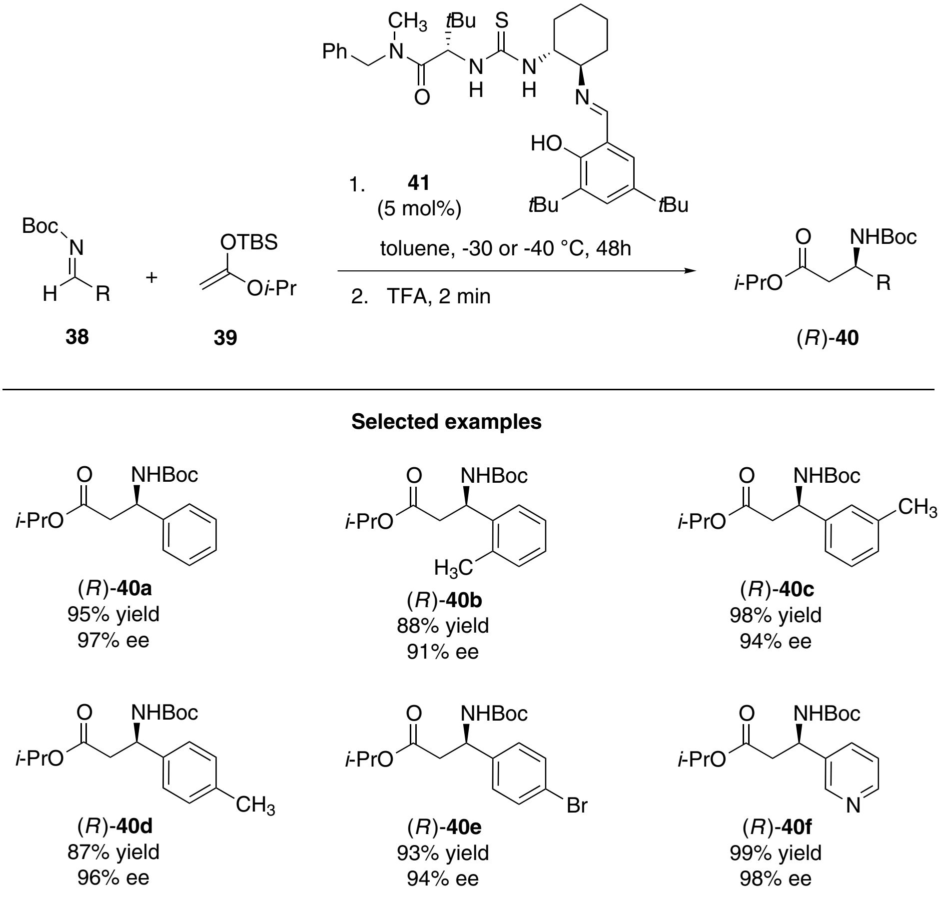
Scheme 5.22

(compared with DMSO and DMF as solvent) and the less satisfactory results for the anti-selective Mannich reaction in the presence of proline as catalyst [34].

An interesting alternative improvement of the process was recently discovered by the Hayashi group, who applied the high pressure induced by water freezing to the direct proline-catalyzed three-component Mannich reaction with a ketone, an aldehyde, and *p*-anisidine [35]. Yields and enantioselectivity were significantly increased, because of the high pressure and low temperature, which are both essential for the positive effect. Substrates which were unreactive under ambient pressure were, furthermore, converted into the corresponding products in good yields. Very recently, the proline-derived 5-pyrrolidin-2-ultetrazole has been found to act as an effective and highly enantioselective organocatalyst, too [38a]. The addition of ketones and isobutyraldehyde to *N*-PMP-substituted α-imino glyoxylate (**33**) gave the corresponding Mannich-products in up to 99% yield, diastereomeric ratio up to 39:1 and with enantioselectivity of up to 99% ee. Additionally, chiral binaphthylphosphoric acids catalyze the direct Mannich reaction of acetyl acetone with *N*-Boc-protected arylimines affording the products in yields up to 99% and with up to 95% ee [38b].

5.2.4
Enantioselective Mannich Reaction Using Silyl Ketene Acetals

In addition to proline, other types of organocatalyst have been found to catalyze the Mannich-type reaction efficiently. The Jacobsen group developed an elegant and highly enantioselective route to *N*-Boc-β-amino acid esters *via* nucleophilic ad-



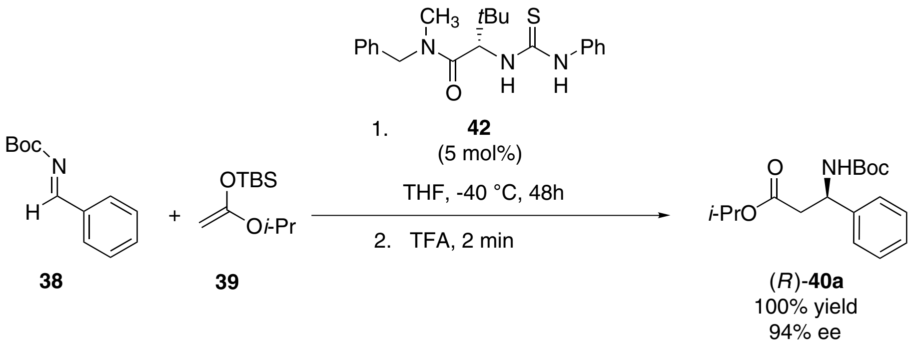
Scheme 5.23

dition of enolates to *N*-Boc-protected imines [36, 37]. Schiff bases, e.g. **41**, which contain a thiourea moiety, were used as catalysts. These types of organocatalyst (and urea analogs thereof) were originally developed for the asymmetric Strecker reaction (see also Section 5.1) and afforded excellent yield and enantioselectivity [40–43]. Application of 5 mol% thiourea **41** in the asymmetric addition of silyl ketene acetals to *N*-Boc-imines **38** led to the desired *β*-amino acid derivatives **40** in both high yield (84–99%) and enantioselectivity (86–98% ee) [36]. Representative examples from this study of the substrate range with aromatic aldimines are shown in Scheme 5.23. For example, *N*-Boc-benzaldimine was converted into (*R*)-**40a** in 95% yield and with 97% ee. Substituted aromatic benzaldimines can also be used. Neither the type nor the position of the substituents significantly affects the high yields and enantioselectivity. Thus, the *o*-, *m*-, and *p*-methyl-substituted aryl *β*-amino acids (*R*)-**40b–d** are obtained in yields of 88–98% and with high enantioselectivity of 91–96% ee. Heteroaryl-containing *β*-amino acid esters are formed

very efficiently as, e.g., shown for the synthesis of (*R*)-**40f** with excellent 99% yield and 98% ee. In addition, naphthylimines are also very good substrates [36].

Imines are, preferably, used in the *N*-Boc-protected form; less electrophilic *N*-allyl and *N*-benzyl imines gave unsuccessful results [36]. The *tert*-butyldimethylsilyl ketene acetals are the most suitable silyl ketene acetal substrates. It should be added that a low temperature is required to suppress an undesired uncatalyzed reaction that leads to racemates.

The Jacobsen group have also focused on optimization of the organocatalyst, and the design of new, simpler catalysts [37], by systematic variation of each modular component of the catalyst, for example the salicylaldimine, diamine, amino acid, and amide. A new catalyst was found, a simple amino acid derivative **42** with less than half the molecular weight and fewer stereogenic centers than the thiourea catalyst **41**. In the presence of this organocatalyst **42**, benzaldimine was converted into the corresponding *β*-phenylalanine derivative (*R*)-**40a** with 100% conversion and 94% ee (Scheme 5.24) [37].



Scheme 5.24

Another type of organocatalyst, which is suitable for the Mannich reaction with ketene silyl acetals, is a chiral binaphthyl phosphoric acid [38c]. Very recently, it has been reported that high enantioselectivity of up to 96% ee can be obtained with this type of catalyst [38c].

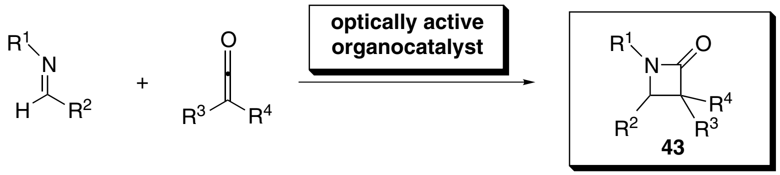
Conclusion

In conclusion, this new organocatalytic direct asymmetric Mannich reaction is an efficient means of obtaining optically active *β*-amino carbonyl compounds. It is worthy of note that besides the enantioselective process, enantio- and diastereoselective Mannich reactions can also be performed, which makes synthesis of products bearing one or two stereogenic centers possible. Depending on the type of acceptor or donor, a broad range of products with a completely different substitution pattern can be obtained. The range of these Mannich products comprises "classic" *β*-amino ketones and esters as well as carbonyl-functionalized *α*-amino acids, and -after reduction-*γ*-amino alcohols.

5.3
β-Lactam Synthesis

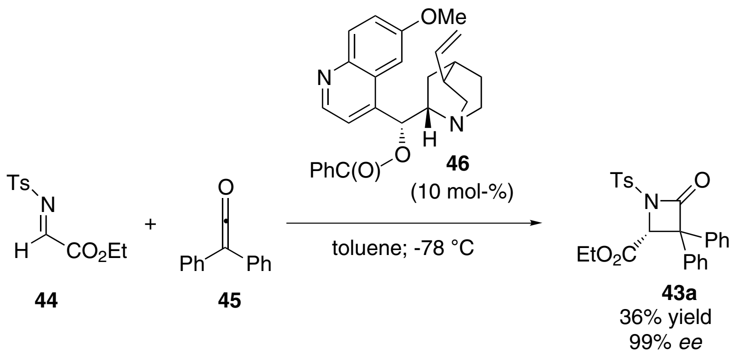
The preparation of optically active β-lactams by asymmetric synthesis is also a topic of major interest, because of the pharmaceutical and biochemical importance of those molecules [44]. A typical and economical route consists of a [2+2]-cycloaddition of a ketene to an imine. Many diastereoselective versions of this reaction type are known [45] as well as catalytic processes involving chiral (metal) catalysts [46, 47] or biocatalysts [48]. A [2+2]-cycloaddition of a ketene to an imine, however, can also be performed very efficiently when applying nucleophilic amines as chiral catalysts [49–60]. Planar-chiral DMAP derivatives have also been found to be suitable catalysts [61].

The first highly enantioselective synthesis of β-lactam ring systems with one or two stereogenic centers was reported by Lectka and co-workers [49, 52]. The concept of this reaction is shown in Scheme 5.25.

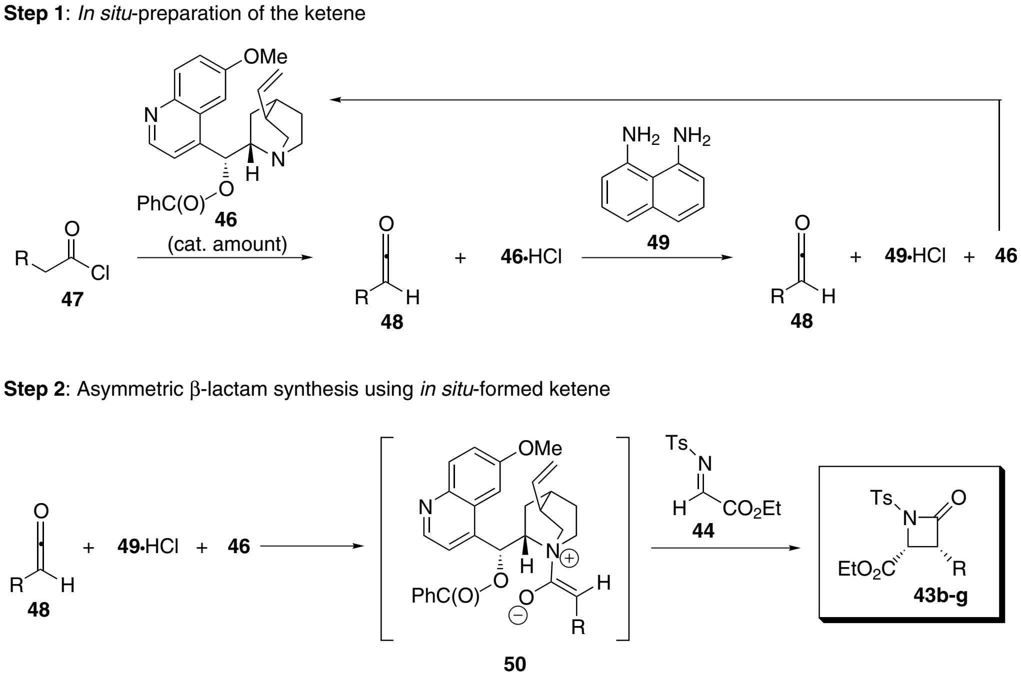


Scheme 5.25

Initially the formation of β-lactams was investigated using diphenylketene as a test substrate. After optimizing the reaction conditions, reaction of ketene **45** with the imine **44** in the presence of benzoylquinine, **46**, (10 mol%) as a catalyst furnished the β-lactam **43a** with excellent enantioselectivity (99% ee, Scheme 5.26) [49, 52], although the yield of 36% was only modest. Interestingly, this excellent enantioselectivity is obtained only when the reaction is performed at high dilution,



Scheme 5.26



Scheme 5.27

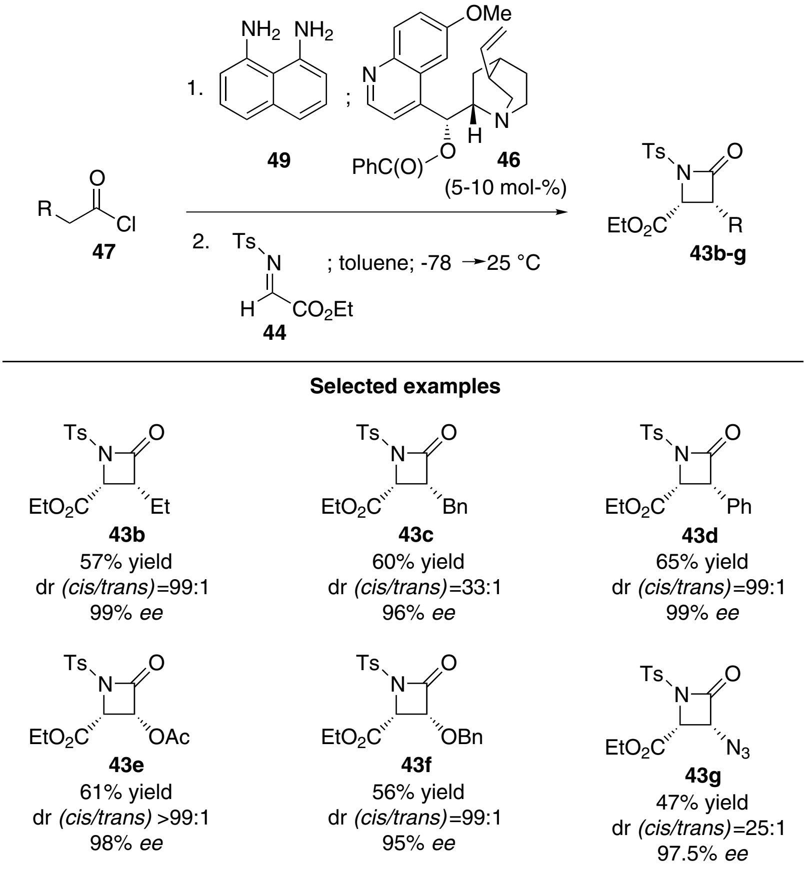
i.e. at concentrations of 0.1 mM or below. In contrast, running the reaction with minimal solvent improves the yield of the process substantially (up to 92%) but leads to a racemic product.

When more reactive monoketenes are used as substrates, access to such compounds is a critical issue. Typically, the monoketenes are prepared *in situ*, starting from the corresponding acid chlorides. Subsequently, in the presence of a chiral organocatalyst, the ketene should react diastereo- and enantioselectively with formation of the *β*-lactam according to Scheme 5.27 [49, 52]. For *in-situ* formation of ketenes, an amine base is required. However, residual amounts of an (achiral) base might catalyze the reaction racemically. Thus, to obtain high enantioselectivity a strong (achiral) organic base "proton sponge" is required as a non-nucleophilic deprotonating agent. The base **49** fulfils this prerequisite, because **49** itself does not lead to any ketene formation. The Lectka group found that a mixture of the base **49** and the organocatalyst **46** is a powerful combination which led to highly enantioselective formation of the desired *β*-lactams. In this reaction the base **49** was made effective as an HCl sink by using the organocatalyst **46** as a "shuttle" base, because **46** is thermodynamically weaker but kinetically active. Thus, a ketene is effectively produced *in situ* with formation of an (achiral) ammonium salt (Scheme 5.27, step 1). Because the organocatalyst **46** is not consumed, and still available as a "free", non-protonated base, **46** can successfully catalyze

subsequent β-lactam formation (Scheme 5.27, step 2). The concept of this two-step process is shown in Scheme 5.27 [49, 52].

Under optimized reaction conditions this two step synthesis for asymmetric preparation of β-lactams is performed as follows. First, the organocatalyst **46** is added as a "shuttle" base to a solution of the acid chloride, **47**, and the "proton sponge", **49**, at low temperature. Within a few minutes the soluble ketene and the hydrochloride salt, **49**·HCl, as a white precipitate, are formed. Subsequently, the imino ester **44** is added to this solution at −78 °C, which results in the asymmetric formation of the β-lactam. Thus, the alkaloid **46** acts both as a dehydrohalogenation agent and as an organocatalyst for subsequent lactam formation [49, 52].

Typically, a catalytic amount of 5–10 mol% of the cinchona alkaloid **46** was used. In general, the desired products of type **43** were obtained in excellent enantio- and diastereoselectivity (95–99% ee, d.r. (cis/trans) ≥ 99:1) whereas the yields were modest – between 36 and 65% (Scheme 5.28). It is worthy of note



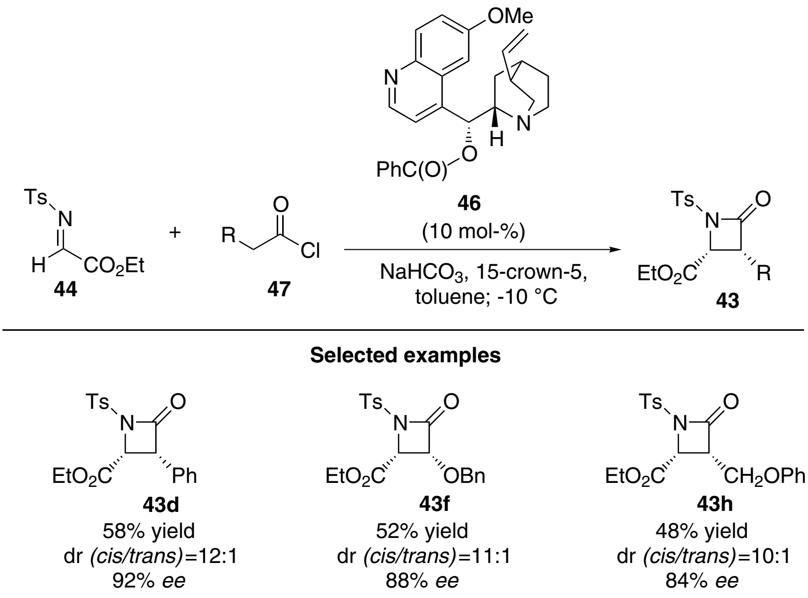
Scheme 5.28

that the Ts protecting group of many products **43** can be subsequently removed by treatment with samarium iodide. An overview of representative synthetic examples of this organocatalytic *β*-lactam formation is given in Scheme 5.28.

This highly enantio- and diastereoselective organocatalytic *β*-lactam synthesis can be used, e.g., for preparation of pharmaceutically interesting products such as **43b**. The formation of *β*-lactam **43b**, which was investigated as an elastase inhibitor [62], proceeds with a diastereomeric ratio of 99:1 and an enantioselectivity of 99% ee (Scheme 5.28) [49, 52].

β-Lactams bearing a heteroatom, e.g., N, O, or Br, in the 3-position have also been synthesized. These compounds are difficult to prepare by other synthetic routes. For example, the 3-oxosubstituted *β*-lactam **43e** was prepared in 61% yield with 98% ee and a diastereomeric ratio of d.r. (cis/trans) > 99:1. In addition, the azido-substituted *β*-lactam **43g** was obtained in 47% yield with 97.5% ee, and a diastereomeric ratio of d.r. (cis/trans) of 25:1. The azido group can be converted, with retention of configuration, to the corresponding amine or amide derivative.

Other successful ketene-generation methods have also been developed which utilize, e.g., sodium hydride, potassium carbonate, or a resin-bound phosphazene as a base [52–55]. In particular procedures with cheap inorganic heterogeneous bases such as sodium hydride, potassium carbonate, and bicarbonate salts are desirable because of their low cost. Although sodium hydride and potassium carbonate can be used for efficient formation of ketenes in asymmetric catalytic *β*-lactam formation [54, 55], use of these inexpensive bases has some drawbacks [53]. NaH must be used with appropriate caution, because of its high hygroscopicity, whereas with potassium carbonate the ketene formation and utilization steps must be performed separately in two vessels, because this base led to racemization or epimerization of the desired products. Interestingly, however, the Lectka group found very recently that bicarbonate salts can be very efficiently used as stoichiometric bases for *in-situ* formation of the desired ketenes for asymmetric *β*-lactam synthesis [53]. *In-situ* synthesis of the ketene starting from the acid chloride in the presence of, e.g., sodium bicarbonate is connected with the formation of NaCl, carbon dioxide and water. The latter can be efficiently removed from the reaction mixture by use of excess of bicarbonate, which then also functions as a drying agent. In screening of different metal bicarbonate salts, sodium bicarbonate was found to be the preferred base. In all experiments a catalytic amount of a crown ether was added to complex the alkali metal, leading to an enhanced solubility. Under optimized conditions the substrate range was investigated with different acid chlorides by conducting the reactions in the presence of a catalytic amount (10 mol%) of **46**. The optically active *β*-lactam products **43** were formed with both high diastereoselectivity (d.r. (cis/trans) ratio 10:1 to 12:1) and enantioselectivity up to 92% ee (Scheme 5.29) [53]. With sodium bicarbonate, however, enantioselectivity was slightly lower compared to the use of the "proton sponge" **49** (see, e.g., results for **43d**, **43f** in Schemes 5.28 and 5.29). Yields were moderate (40–58%, Scheme 5.29). This new route based on use of sodium bicarbonate enables cost-effective synthesis of optically active *β*-lactams without the need for specialized equipment or anhydrous conditions [53].

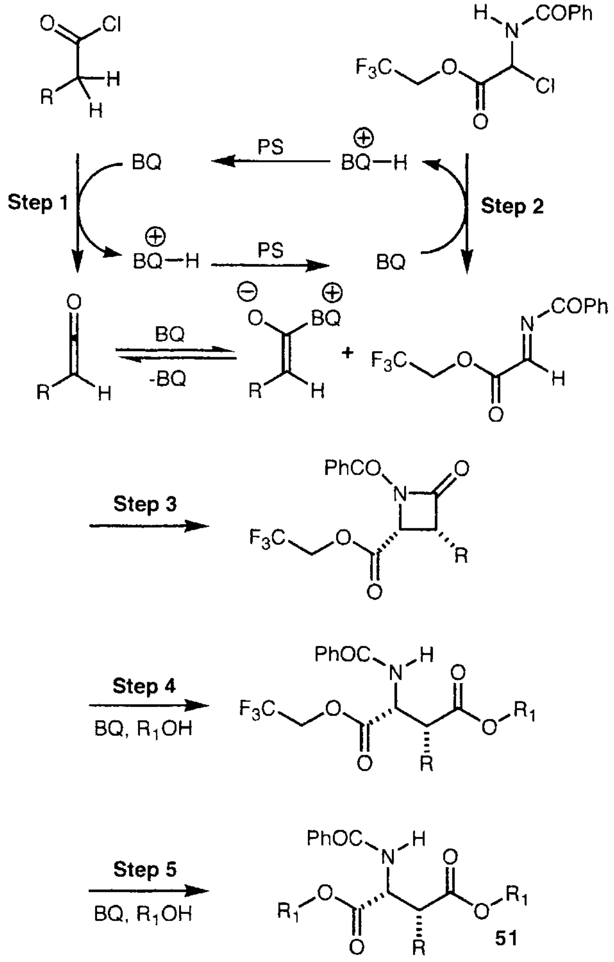


Scheme 5.29

Addition of achiral Lewis acid metal complexes to the developed catalytic system to increase the electrophilicity of the imino ester starting material has also been reported by the Lectka group [56]. The resulting tandem bifunctional catalyst system, consisting of 10 mol% In(OTf)$_3$ and 10 mol% chiral alkaloid organocatalyst, led to higher yields of the β-lactam products while maintaining high enantioselectivity. This bifunctional concept has been extended to the design of chiral Lewis acid complexes in which chiral alkaloid derivatives coordinate to the In(III) metal ion. After optimization, these types of chiral Lewis acid catalyst gave the desired β-lactam products in high yields, high diastereoselectivity, and enantioselectivity up to 99% ee [56].

A very interesting application of the Lectka-type β-lactam synthesis is integration of this catalytic concept into a multi-stage, one-pot procedure for the catalytic asymmetric synthesis of β-substituted aspartic acid derivatives of type **51** [57, 58]. The organocatalyst benzoylquinine (**BQ**, **46**) is capable of performing up to five steps of the reaction pathway, all in one reaction vessel (Scheme 5.30) [58]. At first, the cinchona alkaloid catalyst **BQ** acts as a dehalogenation agent for the preparation of both ketene and *N*-acylimine. Subsequently, **BQ** (**46**) functions as an asymmetric catalyst for formation of the optically active β-lactam, and catalyzes nucleophilic ring-opening. An additional transesterification step can also be catalyzed by the organocatalyst [58].

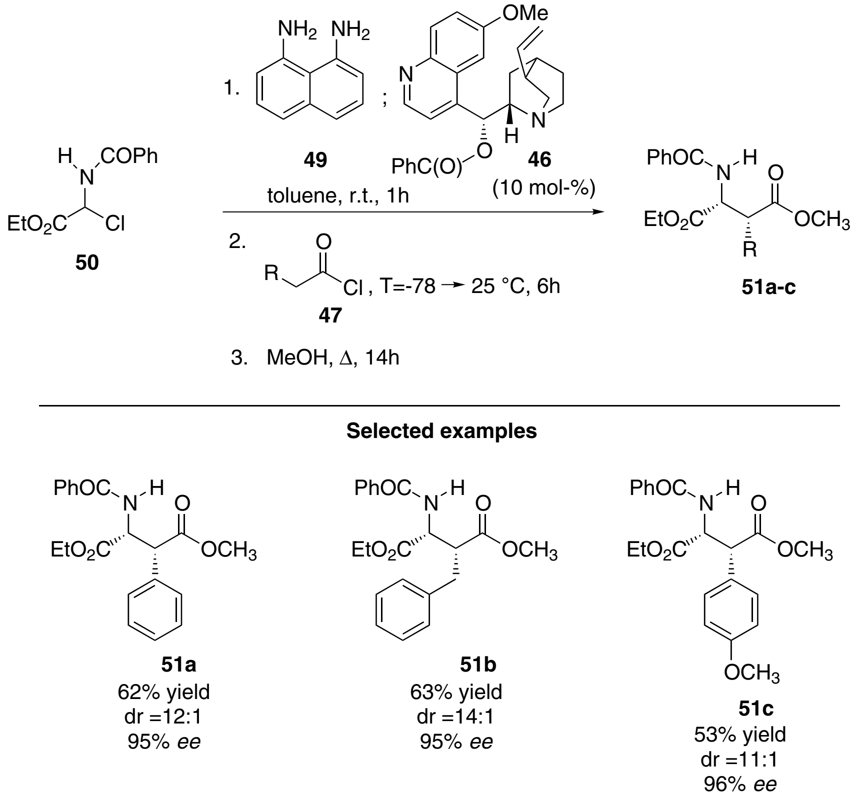
This multi-step one-pot synthetic concept has been applied to the synthesis of a variety of β-amino acids of type **51** in the presence of methanol as ring-opening nucleophile; it was found to be an efficient method leading to the products **51** with high diastereoselectivity (d.r. ratio 10:1 to 14:1) and enantioselectivity (94–96% ee)



Scheme 5.30 (from Ref. [58] with permission of the ACS; **BQ** = benzoylquinine **46**)

[58]. Selected examples are shown in Scheme 5.31. For example, the product **51b** was obtained in 63% yield with a high d.r. ratio of 14:1 and high enantioselectivity of 95% ee. This multi-step one-pot synthesis has also been applied to the synthesis of, e.g., tripeptides and an L-*threo*-β-hydroxyasparagine derivative [58].

The Lectka group also reported an exciting development in this organocatalytic synthesis of β-lactams – application of the concept of "column asymmetric catalysis" [50, 51]. This concept is based, e.g., on two jacketed columns linked together (Scheme 5.32) [50]. The top column is packed with the polymer-supported dehydrohalogenation agent BEMP, which produces the desired ketenes, in high purity, from acid chlorides. In addition to this *in-situ*-formed pure ketene, an imine is

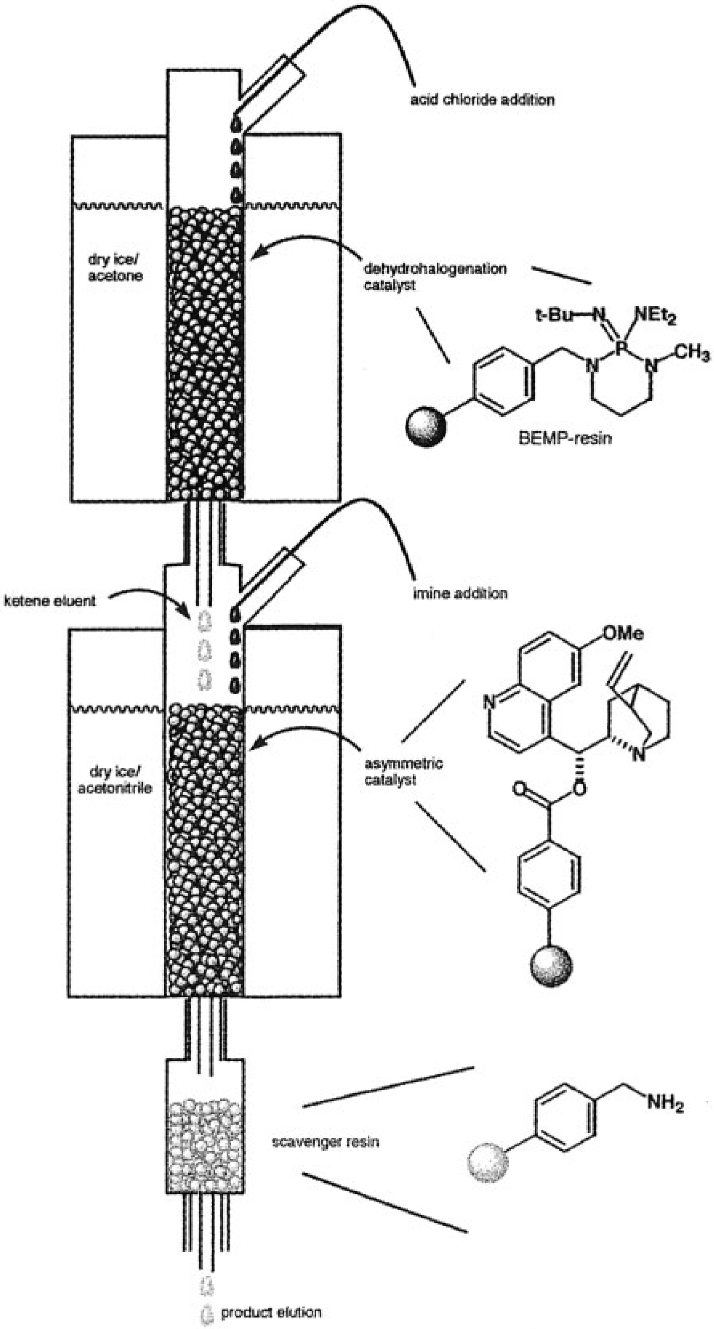


Scheme 5.31

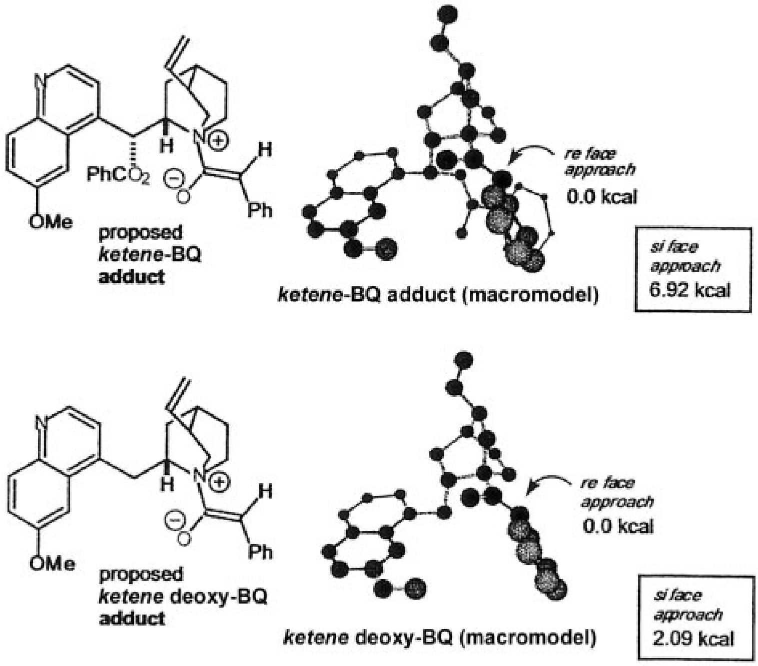
added dropwise to the subsequent middle column which is packed with the solid-phase organocatalyst. In this middle column *β*-lactam formation occurs in the presence of the solid-phase organocatalyst. The reaction mixture is dropped into a bottom column which is packed with a scavenger resin to remove unreacted ketene or imine from the eluent. The eluent contains analytically pure product (**43d**: 91% ee, 65% yield) [50].

The separated catalyst can be re-used at least 20 times with no significant loss of stereoselectivity and yield. Thus this column asymmetric catalysis enables economical production of *β*-lactams guaranteeing both efficient product formation and simple product separation from the catalyst.

This "column asymmetric catalysis" concept (CAC) has also been extended successfully by the Lectka group to other types of column assembly [51]. It should be added that this sequential CAC methodology is not only an efficient tool for a highly asymmetric *β*-lactam synthesis but also looks promising for preparation of other types of chiral compound.



Scheme 5.32 (from Ref. [50] with permission of the ACS)

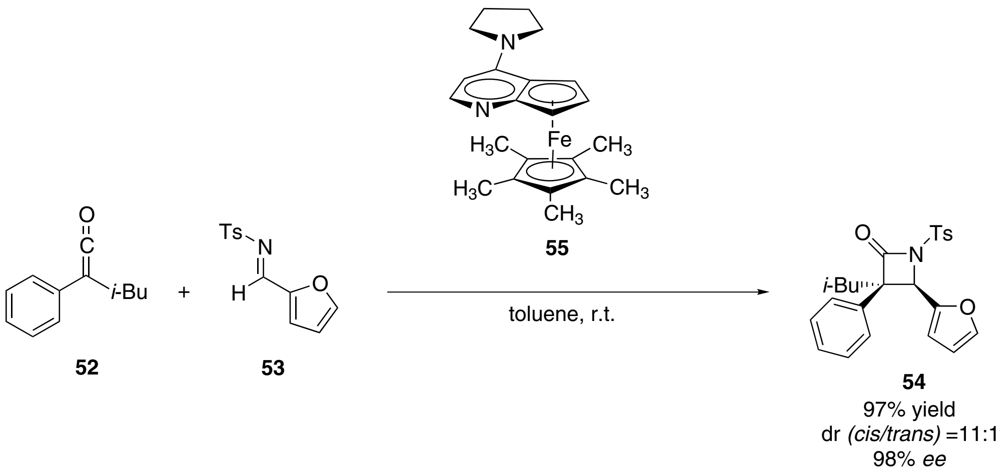


Scheme 5.33 (from Ref. [52] with permission of the ACS; **BQ** = benzoylquinine, **46**)

A very detailed theoretical study on the reaction mechanism, which was supported by synthetic experiments, has also been conducted by the Lectka group [52, 59]. On the basis of molecular mechanics (MM) calculations a model was found which correctly predicts the sense of induction (Scheme 5.33) [52]. This model shows that addition of the electrophilic imine occurs at the re face of the ketene. Very interestingly, the sense of induction is independent of the absolute configuration at the "oxy" stereogenic center bearing the ester oxygen. Even in the absence of this stereogenic center the reaction proceeds with the same sense of induction. A graphical overview of results from this study of the influence of the "oxy" stereogenic center is given in Scheme 5.33 [52].

In contrast, the presence of the methoxy substituent at the aromatic ring is critical for selectivity. This result has been emphasized by experiments using benzoyl cinchonidine (which does not have a methoxy substituent) as a catalyst. In accordance with the theoretical result, a racemic β-lactam product was obtained [52].

Molecular mechanics calculations also led to an explanation of the diastereoselective course of the reaction. Several assemblies of the imino ester, **44**, and the zwitterionic enolate were investigated [52]. In accordance with the experimental results it was found that the assembly leading to the cis diastereomer was of lowest energy. Because the lowest-energy trans assembly is several kilocalories higher, organocatalytic β-lactam formation proceeds with an excellent cis diastereoselectivity.



Scheme 5.34

The Fu group demonstrated that asymmetric addition of ketenes to imines can be also conducted very efficiently when using planar-chiral DMAP-derivatives of type **55** as a catalyst [61]. For example, in the presence of 10 mol% catalyst **55** the desired product **54** was formed in high yield (97%), with high diastereoselectivity (d.r. (cis/trans) = 11:1) and excellent enantioselectivity (98% ee) (Scheme 5.34). The reaction was also found to be very general, tolerating symmetric and non-symmetric ketenes and a variety of imines. Irrespective of the substitution pattern, the resulting *β*-lactam products are formed with high enantioselectivity in the range 81–98% ee [61].

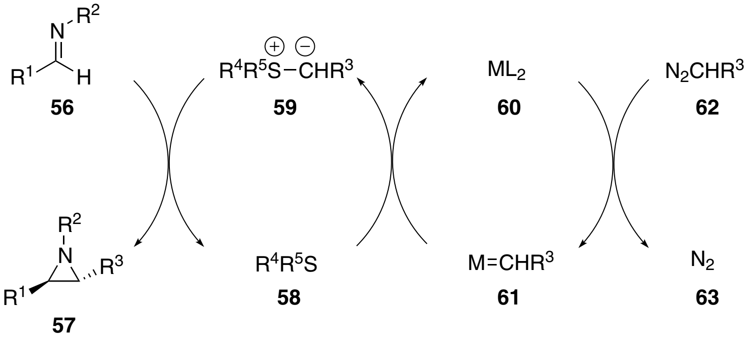
In conclusion, efficient methods are available for synthesis of optically active *β*-lactams by means of enantio- and diastereoselective addition of ketenes to imines. Different (organo-)catalysts have been applied, for example alkaloid-based catalytic systems and planar chiral DMAP-complexes. The enantio- and diastereoselectivity obtained is impressive with, e.g., ee values up to 99% and d.r. (cis/trans) ratios up to >99:1 when Lectka-type catalytic systems are used. Among future challenges might be the design of a trans-diastereoselective process and improvement of chemical yields. In a very recent contribution addressing the latter issue Lectka et al. showed that very good yields (up to 92%) can be achieved by adding a non-chiral Lewis-acid additive. The development of suitable optimized organocatalysts which give products not only with high ee and high diastereomeric ratio but also in high yields, even in the absence of additives, would, nevertheless, still be of interest. A further goal of future activity might be reduction of the amount of catalyst, currently in the range 5–10 mol%. This organocatalytic asymmetric *β*-lactam synthesis developed by Lectka et al. and Fu et al. is certainly, already, a highly practical procedure for efficient preparation of these important target molecules and has a remarkable potential to find applications on larger scale.

5.4 Sulfur Ylide-based Aziridination of Imines

The asymmetric synthesis of optically active aziridines, nitrogen analogs of epoxides, is an important and intensively investigated field [63]. These products are widely used as versatile building blocks in organic synthesis for further transformation [64] and have interesting biological activity which makes them of interest for pharmaceutical applications [65–68]. Numerous efficient methods have been developed for catalytic asymmetric synthesis of aziridines [69], e.g. nitrene transfer to olefins in the presence of metal catalysts or carbene addition to the C=N double bond. Syntheses based on use of imines can be performed *via* addition of chiral metallocarbenes (formed *in situ*) and by chiral Lewis-acid complex-catalyzed aziridination [69]. For the latter concept metal-catalyzed and organocatalytic routes are available. The metal-complex-based aziridination of imines entails use of efficient chiral Lewis acids. In this connection, Wulff and co-workers developed an elegant approach, using a chiral boron complex, which gave products with high diastereoselectivity and enantioselectivity (up to 99% ee) [70]. For the organocatalytic approach a very efficient process based on the sulfur ylide-concept has been developed by the Aggarwal group [71]. The sulfur ylide concept has already been applied by the same group for the epoxidation reaction (Section 6.8). This asymmetric catalytic aziridination concept from the Aggarwal group is based on carbene transfer in the presence of chiral sulfides as organocatalysts (Scheme 5.35).

The required chiral sulfur ylide of type **59** is formed in a reaction with a diazo compound in the presence of an achiral metal catalyst. Subsequently, asymmetric reaction of the chiral ylide **59** with the C=N double bond of the imine proceeds diastereoselectively and enantioselectively, giving the optically active aziridine **57**. The chiral sulfide catalyst released is then used for the next catalytic cycle. The catalytically active species in the asymmetric process is the sulfide, so this concept can also be regarded as an organocatalytic reaction.

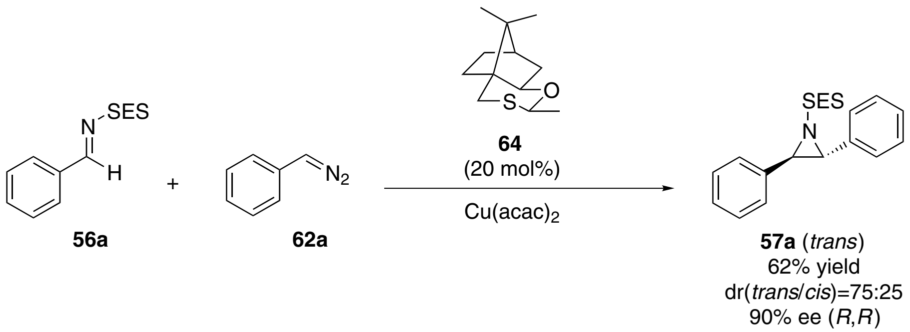
The use of stoichiometric amounts of sulfur ylides in the diastereoselective addition to imines has been recognized for a long time as a means of efficient synthesis



Scheme 5.35

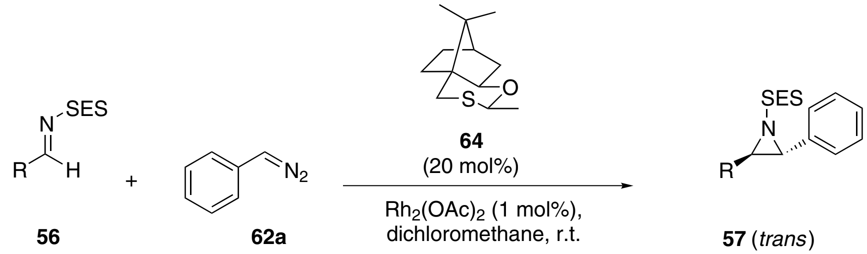
of the corresponding (racemic) aziridines [73–78]. The products obtained from these syntheses are racemates [79]. Extension of this concept to a catalytic diastereoselective synthesis was reported by Dai and co-workers, who used dimethyl sulfide as catalyst [80]. This first example of a catalytic cycle was used for diastereoselective preparation of racemic vinylic aziridines under basic conditions [80].

The first development of an (organo)catalytic and asymmetric sulfur ylide type aziridination reaction, leading to aziridines with high enantiomeric excess, was reported in 1996 by the Aggarwal group [79]. In the presence of stoichiometric amounts of the sulfide **64**, derived from (+)-camphorsulfonyl chloride, the corresponding reaction gave the aziridine *trans*-(*R*,*R*)-**57a** in 55% yield and with high enantioselectivity of 97%. The reaction also proceeds with the lower catalyst loading of 20 mol% sulfide **64**, furnishing the desired aziridine *trans*-(*R*,*R*)-**57a** in somewhat lower (62%) yield and with 90% ee (Scheme 5.36). Irrespective of catalyst loading, a diastereomeric ratio of d.r. (trans/cis) = 75:25 was obtained. It is worthy of note that the quality of the copper complex is critical to this process. The lower enantioselectivity for the lower catalyst loading (90% compared with 95% ee) can be explained in terms of competing non-asymmetric direct addition of the copper carbenoid to the imine. This side-reaction is more significant when catalytic amounts of the sulfide are used.

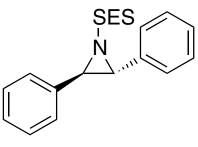


Scheme 5.36

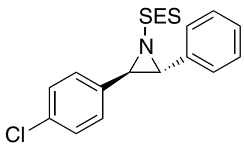
A very detailed investigation of the scope and limitations of this sulfur ylide based aziridination process has also been conducted by the Aggarwal group [81]. Starting with the effect of the solvent, dichloromethane was found to be preferred. Other solvents, e.g. toluene, DME, and acetonitrile resulted in lower yields and enantioselectivity. With regard to the achiral metal component, it was found that $Rh_2(OAc)_4$ is an interesting alternative to $Cu(acac)_2$, because comparable enantioselectivity is obtained, irrespective of the amount of catalyst. This is because of the absence of direct addition of the rhodium carbenoid to the imine as a side-reaction. The substrate range has been studied with several *N*-SES-substituted aldimines (SES = $SO_2CH_2CH_2SiMe_3$). Examples from this study, which are based on use of 20 mol% catalyst and $Rh_2(OAc)_4$ as metal component, are shown in Scheme 5.37. High enantioselectivity was obtained with all aromatic aldimines. For example, the



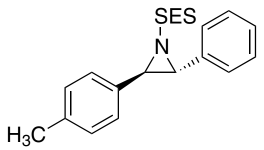
Examples



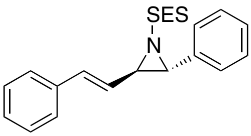
57a (*trans*)
47% yield
dr(*trans*/*cis*)=75:25
95% ee (*R*,*R*)



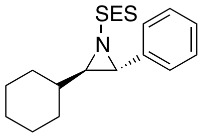
57b (*trans*)
58% yield
dr(*trans*/*cis*)=75:25
88% ee (*R*,*R*)



57c (*trans*)
91% yield
dr(*trans*/*cis*)=75:25
93% ee (*R*,*R*)



57d (*trans*)
62% yield
dr(*trans*/*cis*)=100:20
93% ee (*R*,*R*)

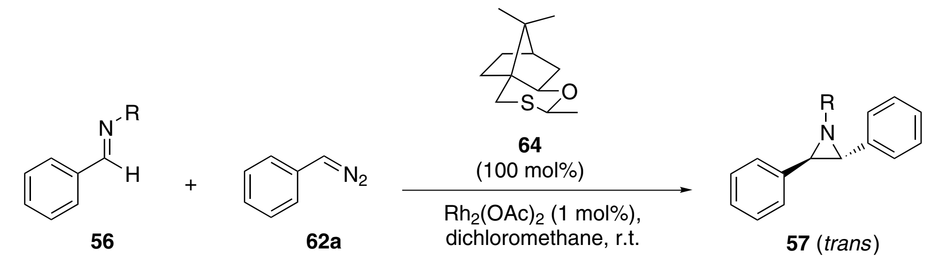


57e (*trans*)
72% yield
dr(*trans*/*cis*)=50:50
89% ee (*R*,*R*)
(100 mol% of sulfide **64** were used in this case)

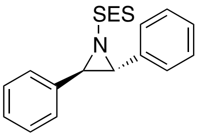
Scheme 5.37

product *trans*-(*R*,*R*)-**57a** was obtained in 47% yield and 95% ee when using 20 mol% sulfide **64**. The diastereomeric ratio was d.r. (trans/cis) = 75:25. In addition, the aldimine derived from cinnamyl aldehyde gave the desired aziridine *trans*-(*R*,*R*)-**57d** in 62% yield with d.r. (trans/cis) = 100:20 and 93% ee. Aliphatic aldimines, also, undergo aziridination (aziridine *trans*-(*R*,*R*)-**57e**, 72% yield, d.r. (trans/cis) = 50:50, 89% ee), although stoichiometric amounts of the sulfide catalyst are required. In contrast, poor results were obtained in the presence of catalytic amounts.

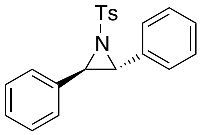
Screening of several sulfide catalysts revealed that sulfide **64** is the most efficient, although other sulfide catalysts also gave high enantioselectivity [81]. To improve the diastereoselectivity further, the effect of an electron-withdrawing *N*-substituent



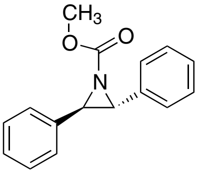
Examples



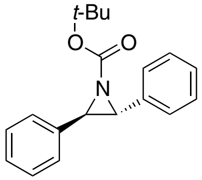
57a (*trans*)
84% yield
dr(*trans*/*cis*)=30:10
95% ee (*R*,*R*)



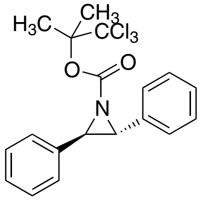
57f (*trans*)
71% yield
dr(*trans*/*cis*)=30:10
92% ee (*R*,*R*)



57g (*trans*)
75% yield
dr(*trans*/*cis*)=60:10
92% ee (*R*,*R*)



57h (*trans*)
60% yield
dr(*trans*/*cis*)=90:10
92% ee (*R*,*R*)



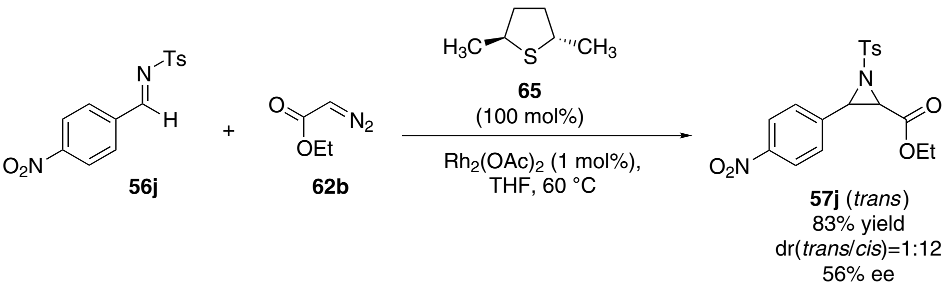
57i (*trans*)
58% yield
dr(*trans*/*cis*)>100:10
92% ee (*R*,*R*)

Scheme 5.38

on diastereo- and enantioselectivity was investigated in the presence of 100 mol% **64** as organocatalyst (Scheme 5.38) [81]. High enantioselectivity was obtained irrespective of the type of *N*-substituent. High diastereoselectivity was obtained for the aziridines **57g–57i**, which are based on the use of aldimines bearing alkoxycarbonyl groups. For example, the aldimines bearing the *N*-Boc and *N*-TcBoc groups gave the corresponding aziridines *trans*-(*R*,*R*)-**57h** and *trans*-(*R*,*R*)-**57i** with diastereomeric ratios of d.r. (trans/cis) = 90:10 and >100:10, respectively [81]. High enantioselectivity of 92% ee was also obtained for both compounds *trans*-(*R*,*R*)-**57h** and *trans*-(*R*,*R*)-**57i**. These *N*-substituents are particularly attractive, because cleavage of these protecting groups is easy and well known.

The range of diazo compounds as substrates was also studied. It was found that

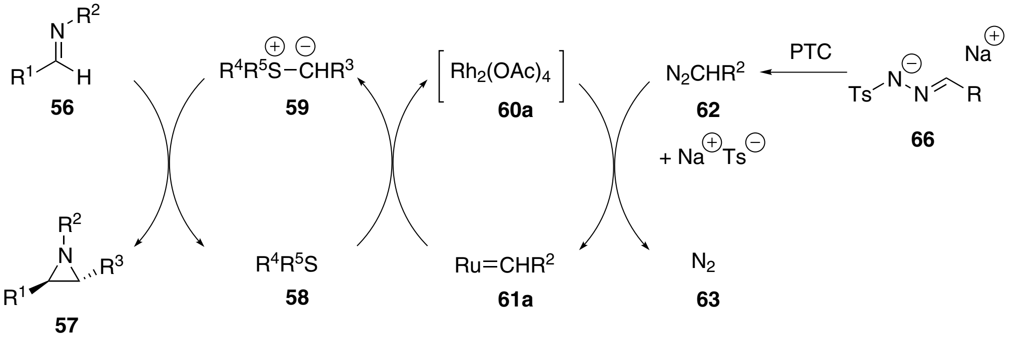
diazo esters and diazo acetamides are suitable diazo substrates when sulfide **65** is used as catalyst [81]. The oxathiane **64**, however, was not compatible with these reactions. For the decomposition of the latter diazo compound higher reaction temperatures are necessary. The enantioselectivity obtained was in the range 30–58% ee. It is worthy of note that the opposite cis diastereomer is formed preferentially when diazoesters are used. A selected example is shown in Scheme 5.39.



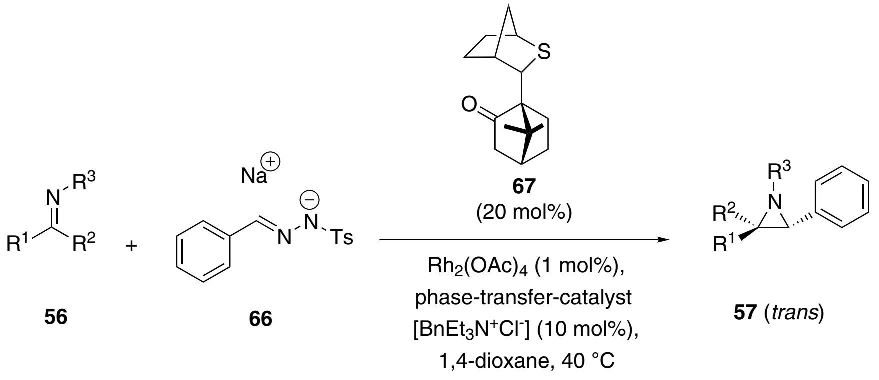
Scheme 5.39

A major improvement addressing the issue of practicability and safety by avoidance of the direct use of (potentially) explosive diazo compounds was recently reported by Aggarwal and co-workers [82, 83]. The direct addition of diazo compounds was replaced by use of suitable precursors which form the desired diazo compound *in situ*. The Aggarwal group developed this concept for the corresponding sulfur ylide type epoxidation (see Section 6.8) [82], and successfully extended it to aziridination [83]. Starting from the tosylhydrazone salt **66** the diazo compound is formed *in situ* under conditions (phase-transfer-catalysis at 40 °C) which were found to be compatible with the sulfur ylide type aziridination [82, 83]. The concept of this improved method, for which sulfide **67** (Scheme 5.41) is the most efficient catalyst, is shown in Scheme 5.40.

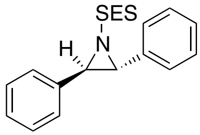
Study of the scope and limitations of the reaction revealed that a broad variety of aldimine is tolerated [83]. These reactions were conducted with a loading of orga-



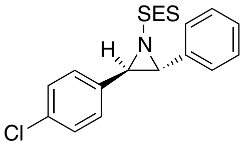
Scheme 5.40



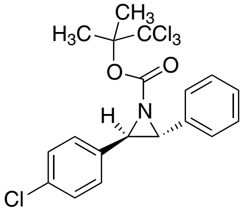
Selected examples



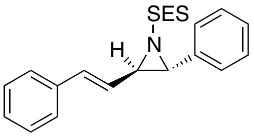
57a (*trans*)
75% yield
dr(*trans*/*cis*)=25:10
94% ee (*R*,*R*)



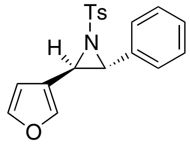
57b (*trans*)
82% yield
dr(*trans*/*cis*)=20:10
98% ee (*R*,*R*)



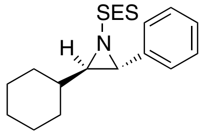
57k (*trans*)
56% yield
dr(*trans*/*cis*)=60:10
94% ee (*R*,*R*)



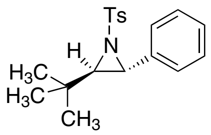
57d (*trans*)
59% yield
dr(*trans*/*cis*)=80:10
94% ee (*R*,*R*)



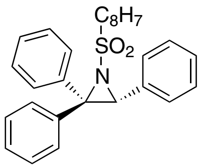
57l (*trans*)
72% yield
dr(*trans*/*cis*)=80:10
95% ee (*R*,*R*)



57e (*trans*)
50% yield
dr(*trans*/*cis*)=25:10
98% ee (*R*,*R*)



57m (*trans*)
53% yield
dr(*trans*/*cis*)=20:10
73% ee (*R*,*R*)



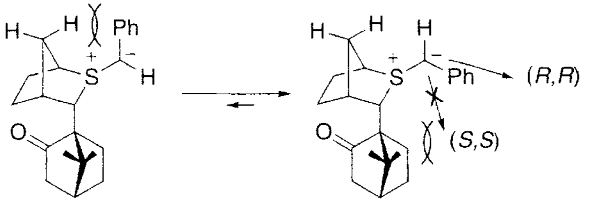
57n
50% yield
84% ee (*R*)

Scheme 5.41

nocatalyst of 20 mol%. An overview of selected examples is given in Scheme 5.41. The highest diastereoselectivity was observed for the aziridination of aldimines derived from cinnamylaldehyde and 3-furfural, leading to the corresponding aziridines *trans*-(*R*,*R*)-**57d** and *trans*-(*R*,*R*)-**57l** with d.r. (trans/cis) = 80:10 in both reactions. The enantioselectivity for the preferred trans diastereomer is also high with 94 and 95% ee, respectively. In general, enantioselectivity is high for aromatic substrates with up to 98% ee, whereas the use of the aliphatic aldimine derived from pivaldehyde gave the major trans aziridine *trans*-(*R*,*R*)-**57m** in 73% ee. In this reaction enantioselectivity was higher (95% ee) for the minor, cis, diastereomer whereas in all other reactions enantioselectivity for the minor cis diastereomers was somewhat lower. The yields obtained for aziridines **57** in Scheme 5.41 were in the range 50–82%. Ketimines are also suitable substrates, as demonstrated in the synthesis of the aziridine (*R*)-**57n** in 50% yield and 84% ee [83]. The catalytic loading can be also reduced, as has been demonstrated for the synthesis of *trans*-(*R*,*R*)-**57a**, which proceeds with the same enantioselectivity and without loss of yield when 5 mol% catalyst **67** is used [74].

An explanation of the remarkably high enantioselectivity of the addition of the (phenyl-stabilized) sulfur ylides to imines has also been reported by the Aggarwal group (Figure 5.2) [82, 83]. The reaction proceeds only *via* the exo-oriented electron pair, leading to the sulfur ylide **68**, which can adopt the conformations **68a** and **68b**. The conformation **68b** is preferred, because of unfavorable steric interactions in **68a**. In conformation **68b** the bulkiness of the camphor-substituent prevents attack from the si side (which would give the (*S*,*S*) enantiomer). Accordingly, formation of the opposite (*R*,*R*) aziridine enantiomer is the preferred pathway, resulting in high excess of this enantiomer.

In summary, sulfur ylide-based aziridination methodology, developed recently by the Aggarwal group, is a new and highly efficient tool for diastereo- and enantioselective synthesis of optically active aziridines. High enantioselectivity up to 98% ee has been obtained. The highest diastereomeric ratio, d.r., was >10:1. Substrate tolerance has also been shown, and the recent improvement replacing the direct use of the diazo compound by *in-situ*-formation starting from a suitable precursor makes the process safer and increases its practicability. Extension of this method to new applications, the development of new sulfide catalysts, and further improvement of catalyst loading are among challenges for the future.

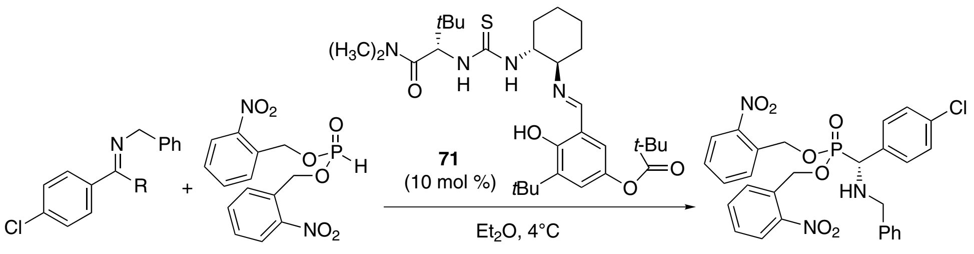


68a **68b**

Fig. 5.2. Schematic explanation of enantioselectivity. (From Ref. [82].)

5.5 Hydrophosphonylation of Imines

The asymmetric catalytic hydrophosphonylation is an attractive approach for the synthesis of optically active α-amino phosphonates [84]. The first example of this type of reaction was reported by the Shibasaki group in 1995 using heterobimetallic lanthanoid catalysts for the hydrophosphonylation of acyclic imines [85a]. This concept has been extended to the asymmetric synthesis of cyclic α-amino phosphonates [85b–d]. Very recently, the Jacobsen group developed the first organocatalytic asymmetric hydrophosphonylation of imines [86]. In the presence of 10 mol% of thiourea-type organocatalyst **71**, the reaction proceeds under formation of α-amino phosphonates **72** in high yield (up to 93%) and with enantioselectivity of up to 99% ee [86]. A selected example is shown in Scheme 5.42. Di-*o*-nitrobenzyl phosphite **70** turned out to be the preferred nucleophile.



Scheme 5.42

References

1 A. Strecker, *Ann. Chem. Pharm.* **1850**, *75*, 27–45.

2 For recent reviews, see: (a) L. Yet, *Angew. Chem.* **2001**, *113*, 900–902; *Angew. Chem. Int. Ed. Engl.* **2001**, *40*, 875–877; (b) H. Gröger, *Chem. Rev.* **2003**, *103*, 2795–2827.

3 For selected excellent contributions of metal-catalyzed asymmetric cyanations, see: (a) M. S. Sigman, E. N. Jacobsen, *J. Am. Chem. Soc.* **1998**, *120*, 5315–5316; (b) C. A. Krueger, K. W. Kuntz, C. D. Dzierba, W. G. Wirschun, J. D. Gleason, M. L. Snapper, A. H. Hoveyda, *J. Am. Chem. Soc.* **1999**, *121*, 4284–4285; (c) M. Takamura, Y. Hamashima, H. Usuda, M. Kanai, M. Shibasaki, *Angew. Chem.* **2000**, *112*, 1716–1718; *Angew. Chem. Int. Ed. Engl.* **2000**, *39*, 1650–1652; (d) H. Ishitani, S. Komiyama, Y. Hasegawa, S. Kobayashi, *J. Am. Chem. Soc.* **2000**, *122*, 762–766.

4 M. S. Iyer, K. M. Gigstad, N. D. Namdev, M. Lipton, *J. Am. Chem.* **1996**, *118*, 4910–4911.

5 M. S. Iyer, K. M. Gigstad, N. D. Namdev, M. Lipton, *Amino Acids* **1996**, *11*, 259–268.

6 E. J. Corey, M. J. Grogan, *Org. Lett.* **1999**, *1*, 157–160.

7 M. S. Sigman, E. N. Jacobsen, *J. Am. Chem. Soc.* **1998**, *120*, 4901–4902.

8 M. S. Sigman, E. N. Jacobsen, *Book of Abstracts, 216th ACS Meeting*, Boston, August 23–27, **1998**.

9 E. N. Jacobsen, M. S. Sigman, PCT Int. Appl. WO9951546, **1999**.

10 M. S. Sigman, P. Vachal, E. N. Jacobsen, *Angew. Chem.* **2000**, *112*, 1336–1338; *Angew. Chem. Int. Ed. Engl.* **2000**, *39*, 1279–1281.

11 J. T. Su, P. Vachal, E. N. Jacobsen, *Adv. Synth. Catal.* **2001**, *343*, 197–200.

12 P. Vachal, E. N. Jacobsen, *J. Am. Chem. Soc.* **2002**, *124*, 10012–10014.

13 P. Vachal, E. N. Jacobsen, *Org. Lett.* **2000**, *2*, 867–870.

14 B. Liu, C. F. Xiaoming, G. Zhang, X. Cui, Y. Jiang, *Synlett* **2001**, 1551–1554.

15 Previously, some Strecker reactions were conducted in the presence of optically active bases and acids, but did not give asymmetric induction, see: Y. Ogata, A. Kawasaki, *J. Chem. Soc B* **1971**, 325–329.

16 For a review about asymmetric syntheses of cyanohydrins, see: R. J. H. Gregory, *Chem. Rev.* **1999**, *99*, 3649–3682.

17 Such type of approach has been reported recently when using Zr based chiral catalysts, see ref. [3d].

18 C. Mannich, W. Krosche, *Arch. Pharm. (Weinheim)* **1912**, *250*, 647–667.

19 For reviews, see: (a) E. F. Kleinmann in: *Comprehensive Organic Synthesis*, Ed.: B. M. Trost, Pergamon Press, New York, 1991, Vol. 2, chapter 4.1; (b) R. M. Williams, J. A. Hendrix, *Chem. Rev.* **1992**, *92*, 889–917.

20 For selected asymmetric metal-catalyzed Mannich-type reactions, see: (a) H. Fujieda, M. Kanai, T. Kambara, A. Iida, K. Tomioka, *J. Am. Chem. Soc.* **1997**, *119*, 2060–2061; (b) S. Kobayashi, H. Ishitani, M. Ueno, *J. Am. Chem. Soc.* **1998**, *120*, 431–432; (c) D. Ferraris, B. Young, M. Sodeoka, *J. Am. Chem. Soc.* **1998**, *120*, 2474–2475; (d) D. Ferraris, B. Young, T. Dudding, T. Lectka, *J. Am. Chem. Soc.* **1998**, *120*, 4548–4549; (e) S. Yamasaki, T. Iida, M. Shibasaki, *Tetrahedron* **1999**, *55*, 8857–8867; (f) K.-i. Yamada, S. J. Harwood, H. Gröger, M. Shibasaki, *Angew. Chem.* **1999**, *111*, 3713–3715; *Angew. Chem. Int. Ed.* **1999**, *38*, 3504–3506; (g) K. Juhl, N. Gathergood, K. A. Jørgensen, *Angew. Chem.* **2001**, *113*, 3083–3085; *Angew. Chem. Int. Ed.* **2001**, *40*, 2995–2997; (h) L. Bernardi, A. S. Gothelf, G. Rita, K. A. Jørgensen, *J. Org. Chem.* **2003**, *68*, 2583–2591.

21 For reviews about the asymmetric Mannich reaction, see: (a) M. Arend, B. Westermann, N. Risch, *Angew. Chem.* **1998**, *110*, 1096–1122; *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 1044–1070; (b) S. E. Denmark, O. J.-C. Nicaise in: *Comprehensive Asymmetric Catalysis* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Heidelberg, **1999**, 923–961; (c) A. Cordova, *Acc. Chem. Res.* **2004**, *37*, 102–112.

22 B. List, *J. Am. Chem. Soc.* **2000**, *122*, 9336–9337.

23 B. List, P. Pojarliev, W. T. Biller, H. J. Martin, *J. Am. Chem. Soc.* **2002**, *124*, 827–833.

24 W. Notz, K. Sakthivel, T. Bui, G. Zhong, C. F. Barbas, III, *Tetrahedron Lett.* **2001**, *42*, 199–201.

25 P. Pojarliev, W. T. Biller, H. J. Martin, B. List, *Synlett* **2003**, 1903–1905.

26 A. Cordova, W. Notz, G. Zhong, J. M. Betancort, C. F. Barbas, III, *J. Am. Chem. Soc.* **2002**, *124*, 1842–1843.

27 A. Cordova, S.-i. Watanabe, F. Tanaka, W. Notz, C. F. Barbas, III, *J. Am. Chem. Soc.* **2002**, *124*, 1866–1867.

28 W. Notz, F. Tanaka, S.-i. Watanabe, N. S. Chowdari, J. M. Turner, R. Thayumanavan, C. F. Barbas, III, *J. Org. Chem.* **2003**, *68*, 9624–9634.

29 S.-i. Watanabe, A. Cordova, F. Tanaka, C. F. Barbas, III, *Org. Lett.* **2002**, *4*, 4519–4522.

30 A. Cordova, C. F. Barbas, III, *Tetrahedron Lett.* **2003**, *44*, 1923–1926.

31 Y. Hayashi, W. Tsuboi, I. Ashimine, T. Urushima, M. Shoji, K. Sakai, *Angew. Chem.* **2003**, *115*, 3805–3808; *Angew. Chem. Int. Ed.* **2003**, *42*, 3677–3680.

32 A. Cordova, *Synlett* **2003**, 1651–1654.

33 A. Cordova, C. F. Barbas, III, *Tetrahedron Lett.* **2002**, *43*, 7749–7752.

34 N. S. Chowdari, D. B. Ramachary, C. F. Barbas, III, *Synlett* **2003**, 1906–1909.

35 Y. Hayashi, W. Tsuboi, M. Shoji, N. Suzuki, *J. Am. Chem. Soc.* **2003**, *125*, 11208–11209.
36 A. G. Wenzel, M. P. Lalonde, E. N. Jacobsen, *J. Am. Chem. Soc.* **2002**, *124*, 12964–12965.
37 A. G. Wenzel, M. P. Lalonde, E. N. Jacobsen, *Synlett*, **2003**, 1919–1922.
38 (a) A. J. A. Cobb, D. M. Shaw, S. V. Ley, *Synlett* **2004**, 558–560; (b) D. Uraguchi, M. Teradd, *J. Am. Chem. Soc.* **2004**, *126*, 5356–5357; (c) T. Akiyama, J. Itoh, K. Yokata, K. Fuchibe, *Angew. Chem. Int. Ed.* **2004**, *43*, 1566–1568.
39 For reviews about applications of ionic liquids as novel green reaction media in organic synthesis, see: (a) T. Welton, *Chem. Rev.* **1999**, *99*, 2071–2083; (b) P. Wasserscheid, W. Keim, *Angew. Chem.* **2000**, *112*, 3926–3945; *Angew. Chem. Int. Ed.* **2000**, *39*, 3772–3789; (c) R. A. Sheldon, *Chem. Commun.* **2001**, 2399–2407.
40 M. S. Sigman, E. N. Jacobsen, *J. Am. Chem. Soc.* **1998**, *120*, 4901–4902.
41 M. S. Sigman, P. Vachal, E. N. Jacobsen, *Angew. Chem.* **2000**, *112*, 1336–1338; *Angew. Chem. Int. Ed. Engl.* **2000**, *39*, 1279–1281.
42 P. Vachal, E. N. Jacobsen, *J. Am. Chem. Soc.* **2002**, *124*, 10012–10013.
43 J. T. Su, P. Vachal, E. N. Jacobsen, *Adv. Synth. Catal.* **2001**, *343*, 197–200.
44 For reviews, see: (a) G. I. Georg (Ed.), *The Organic Chemistry of β-Lactams*, **1993**, VCH Publications, New York; (b) N. De Kimpe in: *Comprehensive Heterocyclic Chemistry II* (Eds.: A. R. Katritzky, C. W. Rees, E. F. V. Scriven, A. Padwa), Vol. 1B, **1996**, Pergamon, Oxford, pp. 507f.
45 For a review, see: C. Palomo, J. M. Aizpurua, I. Ganboa, M. Oiarbide, *Eur. J. Org. Chem.* **1999**, 3223–3235.
46 For the reaction of imines with lithium enolates in the presence of a chelating catalyst, see: (a) H. Fujieda, M. Kanai, A. I. Kambara, K. Tomioka, *J. Am. Chem. Soc.* **1997**, *119*, 2060–2061; (b) T. Kambara, K. Tomioka, *Chem. Pharm. Bull.* **2000**, *48*, 1577–1580.
47 For other type of enantioselective approaches to β-lactams, see: (a) P. Davoli, I. Moretti, F. Prati, H. Alper, *J. Org. Chem.* **1999**, *64*, 518–521; (b) S. Calet, F. Urso, H. Alper, *J. Am. Chem. Soc.* **1989**, *111*, 931–934; (c) M. P. Doyle, A. V. Kalinin, *Synlett* **1995**, 1075–1076.
48 For a biocatalytic approach, see: P. S. J. Cheetham, *Applied Biocatalysis*, **2000**, 2nd ed., Zylepsis, Ltd., Kent, p. 93–152.
49 A. E. Taggi, A. M. Hafez, H. Wack, B. Young, W. J. Drury, III, T. Lectka, *J. Am. Chem. Soc.* **2000**, *122*, 7831–7832.
50 A. M. Hafez, A. E. Taggi, H. Wack, W. J. Drury, III, T. Lectka, *Org. Lett.* **2000**, *2*, 3963–3965.
51 A. M. Hafez, A. E. Taggi, T. Dudding, T. Lectka, *J. Am. Chem. Soc.* **2001**, *123*, 10853–10859.
52 A. E. Taggi, A. M. Hafez, H. Wack, B. Young, D. Ferraris, T. Lectka, *J. Am. Chem. Soc.* **2002**, *124*, 6626–6635.
53 M. H. Shah, S. France, T. Lectka, *Synlett* **2003**, 1937–1939.
54 A. E. Taggi, H. Wack, A. M. Hafez, S. France, T. Lectka, *Org. Lett.* **2002**, *4*, 627–629.
55 A. M. Hafez, A. E. Taggi, H. Wack, J. Esterbrook, T. Lectka, *Org. Lett.* **2001**, *3*, 2049–2051.
56 S. France, H. Wack, A. M. Hafez, A. E. Taggi, D. R. Witsil, T. Lectka, *Org. Lett.* **2002**, *4*, 1603–1605.
57 T. Dudding, A. M. Hafez, A. E. Taggi, T. R. Wagerle, T. Lectka, *Org. Lett.* **2002**, *4*, 387–390.
58 A. M. Hafez, T. Dudding, T. R. Wagerle, M. H. Shah, A. E. Taggi, T. Lectka, *J. Org. Chem.* **2003**, *68*, 5819–5825.
59 A. E. Taggi, A. M. Hafez, T. Dudding, T. Lectka, *Tetrahedron* **2002**, *58*, 8351–8356.
60 For an excellent review, see: S. France, D. J. Guerin, S. J. Miller, T. Lectka, *Chem. Rev.* **2003**, *103*, 2985–3012.
61 B. L. Hodous, G. C. Fu, *J. Am. Chem. Soc.* **2002**, *124*, 1578–1579.
62 R. A. Firestone, P. L. Barker, J. M. Pisano, B. M. Ashe, M. E. Dahlgreen, *Tetrahedron* **1990**, *46*, 2255–2262.
63 For reviews about the asymmetric synthesis of chiral aziridines, see: (a)

D. Tanner, *Angew. Chem.* **1994**, *106*, 625–646; *Angew. Chem., Int. Ed.* **1994**, *33*, 599–619; (b) H. M. I. Osborn, J. Sweeney, *Tetrahedron: Asymmetry* **1997**, *8*, 1693–1715; (c) A.-H. Li, L.-X. Dai, V. K. Aggarwal, *Chem. Rev.* **1997**, *97*, 2341–2372; (d) E. N. Jacobsen in: *Comprehensive Asymmetric Catalysis I–III* (Eds.: Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H.), Springer, Berlin, **1999**, p. 607–620.

64 For reviews about applications of aziridines in organic syntheses, see: (a) W. McCoull, F. A. Davis, *Synthesis* **2000**, 1347–1365; (b) B. Zwanenburg, T. ten Holte in: *Stereoselective Heterocyclic Synthesis III, Topics in Current Chemistry 216* (Ed.: P. Metz), Springer, Berlin, **2001**, p. 93f.; (c) J. B. Sweeney, *Chem. Soc. Rev.* **2002**, 31, 247–258.

65 A. Louw, P. Swart, F. Allie, *Biochem. Pharmacol.* **2000**, *59*, 167–175.

66 T. Burrage, E. Kramer, F. Brown, *Vaccine* **2000**, *18*, 2454–2461.

67 K. Dvorakova, C. M. Payne, M. E. Tome, M. M. Briehl, T. McClure, R. T. Dorr, *Biochem. Pharmacol.* **2000**, 749–758.

68 A. Regueiro-Ren, R. M. Borzilleri, X. Zheng, S.-H. Kim, J. A. Johnson, C. R. Fairchild, F. Y. F. Lee, B. H. Long, G. D. Vite, *Org. Lett.* **2001**, *3*, 2693–2696.

69 For an excellent, very recent review about catalytic asymmetric aziridination, see: P. Müller, C. Fruit, *Chem. Rev.* **2003**, *103*, 2905–2919.

70 J. C. Antilla, W. D. Wulff, *J. Am. Chem. Soc.* **1999**, *121*, 5099–5100.

71 For a review about the Aggarwal-type epoxidation and azirination reactions, see: V. K. Aggarwal, J. G. Ford, A. Thompson, J. Studley, R. V. H. Jones, R. Fieldhouse, *Current Trends in Organic Synthesis, Proceedings of the International Conference on Organic Synthesis, 12th, Venezia, June 28–July 2, 1998*, Kluwer Academic/Plenum Publishers, New York, **1999**, 191–197.

72 For a review from the Aggarwal group about their sulfur ylide chemistry, see: V. K. Aggarwal, *Synlett* **1998**, 329–336.

73 V. Franzen, H. E. Driesen, *Chem. Ber.* **1963**, *96*, 1881–1890.

74 E. J. Corey, M. Chaykovsky, *J. Am. Chem. Soc.* **1965**, *87*, 1353–1364.

75 R. S. Tewari, A. K. Awasthi, A. Awasthi, *Synthesis* **1983**, 330–331.

76 A.-H. Li, L.-X. Dai, X.-L. Hou, *J. Chem. Soc., Chem. Commun.* **1996**, 491–492.

77 A.-H. Li, L.-X. Dai, X.-L. Hou, *J. Chem. Soc., Perkin Trans 1* **1996**, 2725–2729.

78 A.-H. Li, L.-X. Dai, X.-L. Hou, M.-B. Chen, *J. Org. Chem.* **1996**, *61*, 4641–4648.

79 V. K. Aggarwal, A. Thompson, R. V. H. Jones, M. C. H. Standen, *J. Org. Chem.* **1996**, *61*, 8368–8369.

80 A.-H. Li, L.-X. Dai, X.-L. Hou, *J. Chem. Soc., Perkin Trans 1* **1996**, 867–869.

81 V. K. Aggarwal, M. Ferrara, C. J. O'Brien, A. Thompson, R. V. H. Jones, R. Fieldhouse, *J. Chem. Soc., Perkin Trans 1* **2001**, 1635–1643.

82 V. K. Aggarwal, E. Alonso, G. Hynd, K. M. Lydon, M. J. Palmer, M. Porcelloni, J. R. Studley, *Angew. Chem.* **2001**, *113*, 1479–1482; *Angew. Chem., Int. Ed.* **2001**, *40*, 1430–1433.

83 V. K. Aggarwal, E. Alonso, G. Fang, M. Ferrara, G. Hynd, M. Porcelloni, *Angew. Chem.* **2001**, *113*, 1482–1485; *Angew. Chem., Int. Ed.* **2001**, *40*, 1433–1436.

84 For a review, see: H. Gröger, B. Hammer, *Chem. Eur. J.* **2000**, *6*, 943–948.

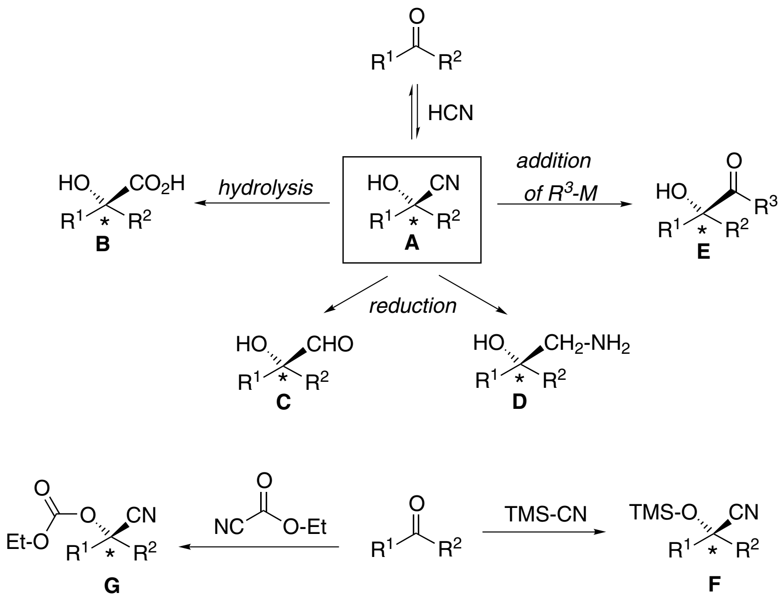
85 (a) H. Sasai, S. Arai, Y. Tahara, M. Shibasaki, *J. Org. Chem.* **1995**, *60*, 6656–6657; (b) H. Gröger, Y. Saida, S. Arai, J. Martens, H. Sasai, M. Shibasaki, *Tetrahedon Lett.* **1996**, *37*, 9291–9292; (c) H. Gröger, Y. Saida, H. Sasai, K. Yamaguchi, J. Martens, M. Shibasaki, *J. Am. Chem. Soc.* **1998**, *120*, 3089–3103; (d) I. Schlemminger, Y. Saida, H. Gröger, W. Maison, N. Durot, H. Sasai, M. Shibasaki, J. Martens, *J. Org. Chem.* **2000**, *65*, 4818–4825.

86 G. D. Joly, E. N. Jacobsen, *J. Am. Chem. Soc.* **2004**, *126*, 4102–4103.

6
Nucleophilic Addition to C=O Double Bonds

6.1
Hydrocyanation

The addition of hydrogen cyanide to a carbonyl group results in the formation of an α-hydroxy nitrile, a so-called cyanohydrin (**A**, Scheme 6.1) [1]. Compounds of this type have in many instances served as intermediates in the synthesis of, e.g., α-hydroxy acids **B**, α-hydroxy aldehydes **C**, β-amino alcohols **D**, or α-hydroxy ketones **E** (Scheme 6.1) [1]. In all these secondary transformations of the cyanohydrins **A**, the stereocenter originally introduced by HCN addition is preserved. Consequently, the catalytic asymmetric addition of HCN to aldehydes and ketones is a synthetically very valuable transformation. Besides addition of HCN, this chapter also covers the addition of trimethylsilyl cyanide and cyanoformate to car-



Scheme 6.1

Asymmetric Organocatalysis. Albrecht Berkessel and Harald Gröger
Copyright © 2005 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim
ISBN: 3-527-30517-3

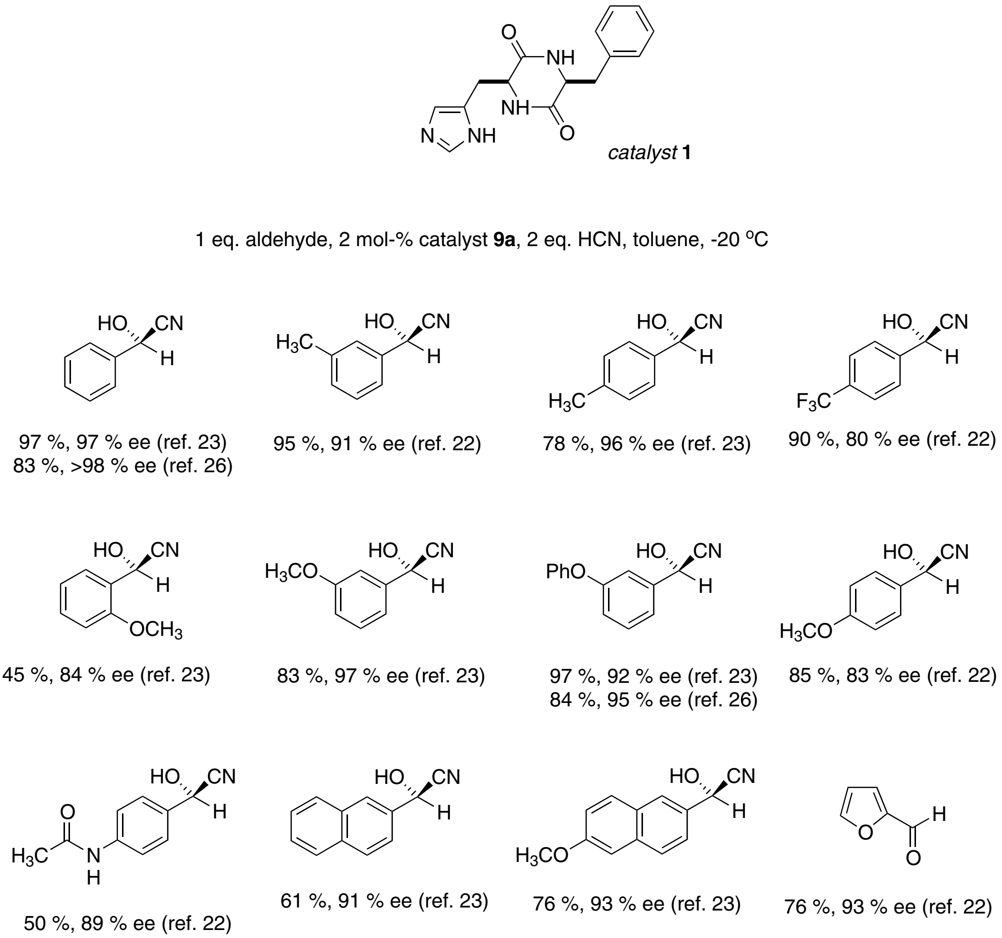
bonyl compounds, resulting in the formation of *O*-silylated cyanohydrins (**F**) and cyanohydrin-*O*-carbonates (**G**), respectively (Scheme 6.1).

Hydrocyanation is, in fact, one of the first examples of asymmetric organocatalysis in general. As early as 1912, Bredig and Fiske reported that addition of HCN to benzaldehyde is accelerated by the alkaloids quinine and quinidine, and that the resulting cyanohydrins are optically active and of opposite chirality [9, 10]. It was, furthermore, realized that prolonged reaction times resulted in loss of optical activity, i.e. racemization. Later (mainly kinetic) work by Prelog and Wilhelm [11], H. and E. Albers [12], and Hustedt and Pfeil [13] was aimed at elucidating the mechanism of this intriguing early example of asymmetric organocatalysis. Unfortunately, for preparative purposes, the optical yields achieved in these examples were in the range $\leq$ 10% [14]. Optical yields up to 33% were achieved by Jackson et al. when crystalline inclusion complexes of aldehydes with β-cyclodextrin were treated with HCN [17].

A real breakthrough was the discovery of the cyclic peptide **1** shown in Scheme 6.2. In 1981 Inoue et al. reported that this cyclic dipeptide – readily available from L-histidine and L-phenylalanine – catalyzed the addition of HCN to benzaldehyde with up to 90% ee [18–20]. Later reaction conditions were optimized and more than fifty aromatic and aliphatic aldehydes have been tested as substrates [8, 16, 18–24]. A selection of the cyanohydrins formed with >80% ee is shown in Scheme 6.2. The cyanohydrins produced by **1** are generally of the *R* configuration.

This initial observation by Inoue et al. triggered intensive research in this area. Most of the efforts were dedicated to structural variation of the catalyst and to elucidation of the catalytic mechanism. With regard to the former, the many structural variations produced mainly confirmed **1** as the optimum catalyst. Variation of the aromatic amino acids involved [25, 26], side-chain methylation and/or modification [27], *N*-methylation [28], etc., all afforded catalysts of lower selectivity. In contrast, incorporation of α-Me-Phe led to diketopiperazines of activity and selectivity comparable with those derived from non-methylated Phe (for example **1**) [29]. Similarly, attachment to Merrifield-resin or polysiloxane polymers proved detrimental to the enantioselectivity of the Inoue-catalyst **1** [30, 31]. Upon incorporation into a silicon based sol-gel glass matrix, however, the excellent enantioselectivity of the cyclic peptide **1** is preserved, and separation of the spent catalyst can easily be achieved by, e.g., filtration, centrifugation or simply decantation [32]. Unfortunately, further catalytic cycles afforded much lower ee (ca. 30–35% max.) [32].

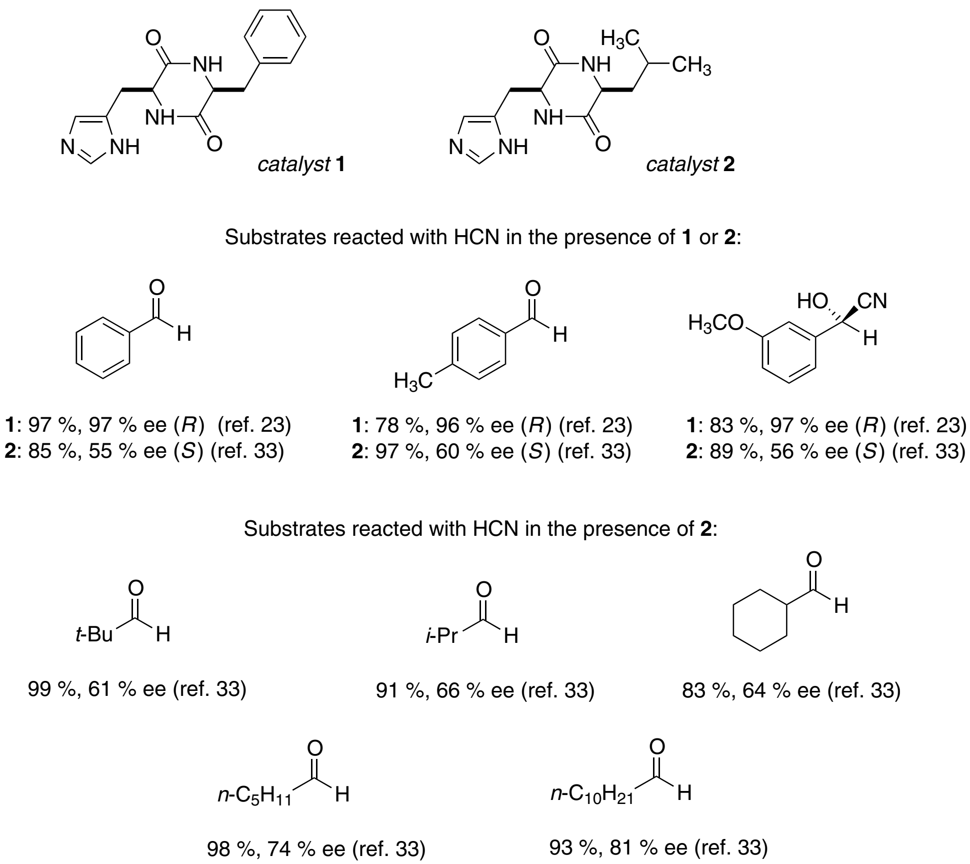
The Inoue-catalyst **1** tolerates exchange of phenylalanine for leucine, affording the catalytically active diketopiperazine cyclo-(*S*)-His-(*S*)-Leu (**2**, Scheme 6.3) [33]. As shown in Scheme 6.3, addition of HCN to benzaldehyde and derivatives can be catalyzed by both **1** and **2**. It should, however, be noted that the configurations of the cyanohydrins obtained were opposite, depending on whether **1** or **2** was employed as catalyst. With aliphatic aldehydes the diketopiperazine **1** generally affords rather poor enantioselectivity (< 50% ee) [19]. In contrast, catalyst **2** afforded ee as high as 81% for aliphatic aldehydes (Scheme 6.3) [33]. The absolute configuration of the product cyanohydrin was determined only for *n*-butyraldehyde as substrate (not shown in Scheme 6.3) and found to be *R* [33].



Scheme 6.2

6.1.1
The Mechanism of the Reaction

Many studies, mainly by spectroscopic methods and calculation, have been devoted to the conformational behavior of the Inoue catalyst **1** (and **2**) and its interactions with HCN and the substrate aldehydes [26, 34–36]. As noted originally by Inoue et al., however, the diketopiperazine **1** does not have catalytic activity and selectivity in homogeneous solution, i.e. in molecular dispersion. Instead, the diketopiperazine **1** is a heterogeneous catalyst – the active/selective state is a gel which forms, for example, in benzene or toluene, or just a suspension (e.g. in ether). As a consequence, catalyst performance is strongly influenced by the amorphous or crystalline character of the diketopiperazine from which the gel is formed. The best performance was achieved when amorphous materials were employed. The latter can



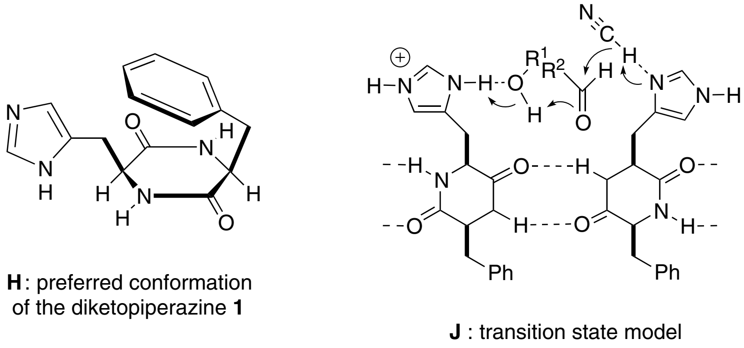
Scheme 6.3

be prepared, *inter alia*, by rapid addition of methanol solutions of **1** to either water [18, 26] or ether [37], resulting in the precipitation of amorphous **1**. Kinetic studies by Shvo et al. further supported the involvement of aggregates in the active form of the catalyst **1**. On the basis of the kinetic order of two found for the catalyst **1**, the authors postulated that in the polymeric gel, two adjacent diketopiperazine molecules form the catalytic "micro-machinery" [38].

The situation is further complicated by chiral autoinduction, first reported by Danda et al. for the hydrocyanation of 3-phenoxybenzaldehyde [39]. It was found that the enantiomeric excess of the product increases with reaction time, and that addition of small amounts of optically pure cyanohydrin at the beginning of the reaction led to high ee of the bulk product, irrespective of catalyst ee. It was concluded that the active catalyst is *not* the diketopiperazine alone but a 1:1 aggregate with the product cyanohydrin of the opposite configuration (e.g. (*R*,*R*)-**1** plus *S*-mandelonitrile) [39]. Lipton et al. later developed a mathematical model for this effect and exploited it to improve the enantioselectivity of the hydrocyanation of

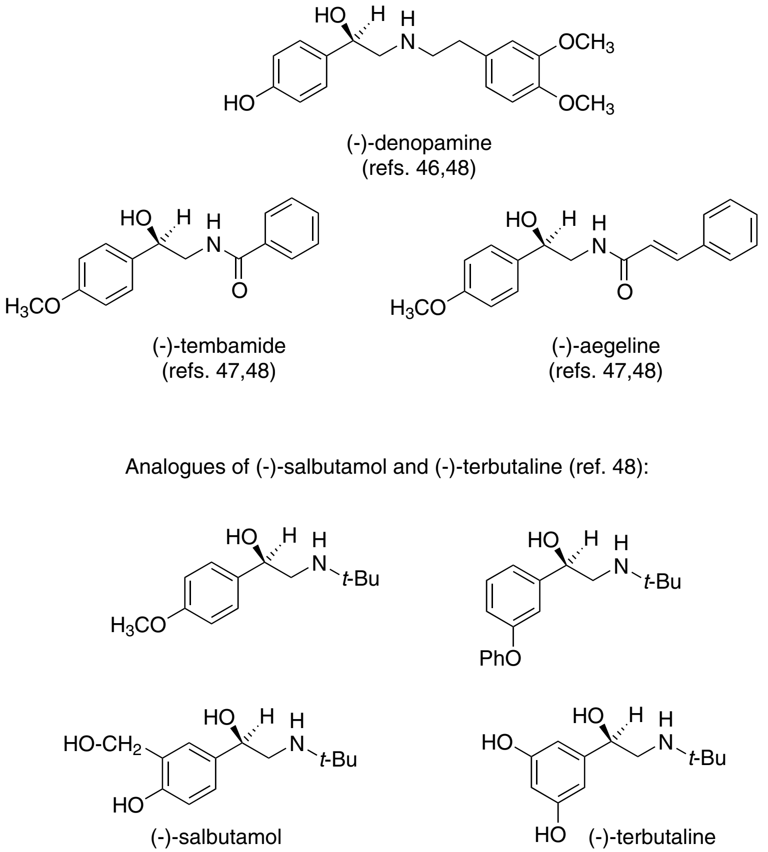
several "problematic" substrates by as much as 20% ee [40]. The cyanohydrin added at the beginning of the reaction does not need to be the one produced by the reaction, a beneficial effect was even observed on addition of the achiral acetone cyanohydrin. Even some non-cyanohydrin additives, e.g. 1-phenylethanol, have the same effect [40].

Several studies have tackled the structure of the diketopiperazine **1** in the solid state by spectroscopic and computational methods [38, 41, 42]. De Vries et al. studied the conformation of the diketopiperazine **1** by NMR in a mixture of benzene and mandelonitrile, thus mimicking reaction conditions [43]. North et al. observed that the diketopiperazine **1** catalyzes the air oxidation of benzaldehyde to benzoic acid in the presence of light [44]. In the latter study oxidation catalysis was interpreted to arise via a His-aldehyde aminol intermediate, common to both hydrocyanation and oxidation catalysis. It seems that the preferred conformation of **1** in the solid state resembles that of **1** in homogeneous solution, i.e. the phenyl substituent of Phe is folded over the diketopiperazine ring (**H**, Scheme 6.4). Several transition state models have been proposed. To date, it seems that the proposal by Hua et al. [45], modified by North [2a] (**J**, Scheme 6.4) best combines all the experimentally determined features. In this model, catalysis is effected by a diketopiperazine dimer and depends on the proton-relay properties of histidine (imidazole). R^1-OH represents the alcohol functionality of either a product cyanohydrin molecule or other hydroxylic components/additives. The close proximity of both R^1-OH and the substrate aldehyde R^2-CHO accounts for the stereochemical induction exerted by R^1-OH, and thus effects the asymmetric autocatalysis mentioned earlier.



Scheme 6.4

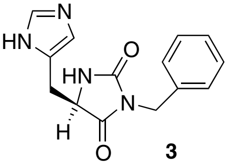
In summary, much information has been gathered by different methods, but there is still room for improvement of the substrate spectrum of the diketopiperazine catalyst **1** and for detailed understanding of the mechanism – and thus predictability – of this fairly complex heterogeneous catalyst system. Nevertheless, enantiomerically pure cyanohydrins – prepared with the aid of **1** – have already been used for synthesis of several natural product (and other) target molecules



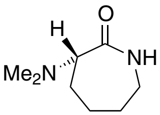
Scheme 6.5

[46–48]. Some examples are depicted in Scheme 6.5. Unfortunately, the 3,4- and 3,5-disubstituted benzaldehydes needed for the synthesis of the pharmaceuticals (−)-salbutamol or (−)-terbutaline performed only poorly (variable yields, ee $\leq$ 50%) in the diketopiperazine-catalyzed hydrocyanation [48].

The search for other amino acid-based catalysts for asymmetric hydrocyanation identified the imidazolidinedione (hydantoin) **3** [49] and the ε-caprolactam **4** [21]. Ten different substituents on the imide nitrogen atom of **3** were examined in the preparation, from 3-phenoxybenzaldehyde, of (*S*)-2-hydroxy-2-(3-phenoxyphenyl)acetonitrile, an important building block for optically active pyrethroid insecticides. The *N*-benzyl imide **3** finally proved best, affording the desired cyanohydrin almost quantitatively, albeit with only 37% enantiomeric excess [49]. Interestingly, the catalyst **3** is active *only* when dissolved homogeneously in the reaction medium (as opposed to the *heterogeneous* catalyst **1**) [49]. With the lysine derivative **4** the cyanohydrin of cyclohexane carbaldehyde was obtained with an enantiomeric excess of 65% by use of acetone cyanohydrin as the cyanide source [21].



3



4

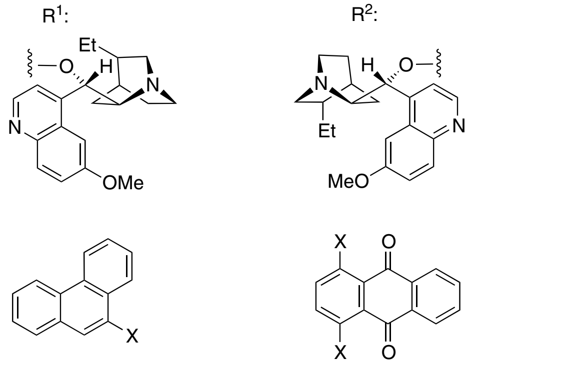
It was mentioned at the beginning of this chapter that alkaloids were among the first catalysts to be used for asymmetric hydrocyanation of aldehydes. More recent work by Tian and Deng has shown that the pseudo-enantiomeric alkaloid derivatives **5**/**6** and **7**/**8** catalyze the asymmetric addition of ethyl cyanoformate to aliphatic ketones (Scheme 6.6) [50]. It is believed that the catalytic cycle is initiated by the alkaloid tertiary amine reacting with ethyl cyanoformate to form a chiral cyanide/acylammonium ion pair, followed by addition of cyanide to the ketone and acylation of the resulting cyanoalkoxide. Potentially, the latter reaction step occurs with dynamic kinetic resolution of the cyano alkoxide intermediate [50]. As summarized in Scheme 6.6, the cyanohydrins of α,α-dialkylated and α-acetal ketones were obtained with quite remarkable enantiomeric excess. Clearly the pseudo-enantiomeric catalyst pairs **5**/**6** and **7**/**8** afford products of opposite configuration. Catalyst loadings were in the range 10–35 mol%.

Deng et al. later found that dimeric cinchona alkaloids such as $(DHQ)_2AQN$ (**8**, Scheme 6.6) and $(DHQD)_2PHAL$ (**9**, Scheme 6.7) – both well known as ligands in the Sharpless asymmetric dihydroxylation and commercially available – also catalyze the highly enantioselective cyanosilylation of acetal ketones with TMSCN [51]. As summarized in Scheme 6.7, several α-acetal ketones were converted to the corresponding cyanohydrin TMS-ethers with 90–98% ee at catalyst loadings of 2–20 mol%.

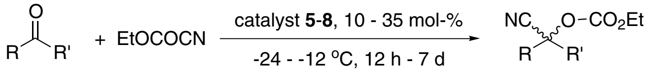
In 2000, Kagan and Holmes reported that the mono-lithium salt **10** of (*R*)- or (*S*)-BINOL catalyzes the addition of TMS-CN to aldehydes (Scheme 6.8) [52]. The mechanism of this reaction is believed to involve addition of the BINOLate anion to TMS-CN to yield an activated hypervalent silicon intermediate. With aromatic aldehydes the corresponding cyanohydrin-TMS ethers were obtained with up to 59% ee at a loading of only 1 mol% of the remarkably simple and readily available catalyst. Among the aliphatic aldehydes tested cyclohexane carbaldehyde gave the best ee (30%). In a subsequent publication the same authors reported that the salen mono-lithium salt **11** catalyzes the same transformation with even higher enantioselectivity (up to 97%; Scheme 6.8) [53]. The only disadvantage of this remarkably simple and efficient system for asymmetric hydrocyanation of aromatic aldehydes seems to be the very pronounced (and hardly predictable) dependence of enantioselectivity on substitution pattern. Furthermore, aliphatic aldehydes seem not to be favorable substrates.

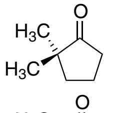
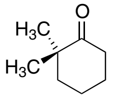
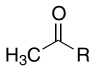
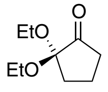
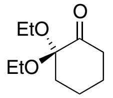
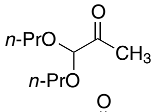
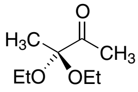
Conclusions

Asymmetric hydrocyanation is a reaction of high synthetic importance. The development of preparatively viable methodology during the last two decades has seen a

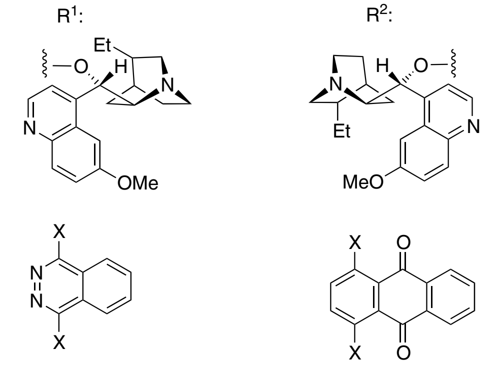


catalyst **5**: X = R[1] [DHQD-PHN]
catalyst **6**: X = R[2] [DHQ-PHN]
catalyst **7**: X = R[1] [$(DHQD)_2$-AQN]
catalyst **8**: X = R[2] [$(DHQ)_2$-AQN]



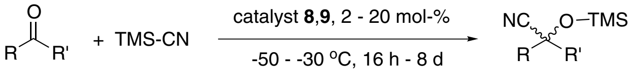
Substrate ketone		Catalyst (mol-%)	Time [d]	Conversion [%]	Yield [%]	ee [%]
		**7** (15)	2	68	66	97
		8 (15)	4	79	76	95
		**7** (20)	4	65	62	91
		8 (30)	5	56	53	92
	R = *n*-pentyl	**7** (20)	0.5	59	54	56
	R = *t*-Bu	**7** (30)	5	58	55	88
	R = *c*-hexyl	**8** (20)	5	55	52	87
		**5** (10)	7	quant.	99	94
		6 (30)	4	83	80	95
		**5** (35)	5	82	78	96
		**5** (30)	4	90	86	96
		**5** (35)	4	68	65	90

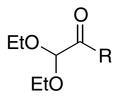
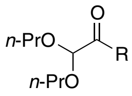
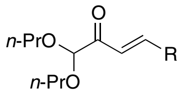
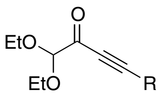
Scheme 6.6



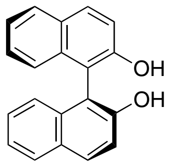
catalyst **9**:
X = R[1] [(DHQD)$_2$-PHAL]

catalyst **8**:
X = R[2] [(DHQ)$_2$-AQN]

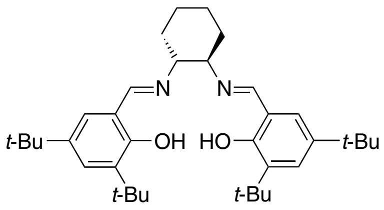


Substrate ketone		Catalyst (mol-%)	Time [h]	Yield [%]	ee [%]
	R = Ph	**8** (2)	19	98	90
	R = 4-MeO-Ph	**8** (2)	18	94	97
	R = 4-Cl-Ph	**8** (2)	18	96	98
	R = 4-Cl-Ph	**9** (10)	40	99	94
	R = *n*-Bu	**8** (5)	18	92	90
	R = *i*-Pr	**8** (20)	94	81	94
	R = Me	**8** (2)	46	97	92
	R = Me	**9** (5)	88	95	96
	R = Bn	**8** (20)	24	96	97
	R = Ph	**8** (2)	16	93	91
	R = 4-MeO-Ph	**8** (2)	18	92	90
	R = 4-MeO-Ph	**9** (10)	21	96	92
	R = 4-Cl-Ph	**8** (2)	18	95	92
	R = 3-pyridinyl	**8** (2)	18	97	93
	R = Ph	**8** (2)	19	93	96
	R = Ph	**9** (10)	21	96	93
	R = *n*-Bu	**8** (2)	18	94	95

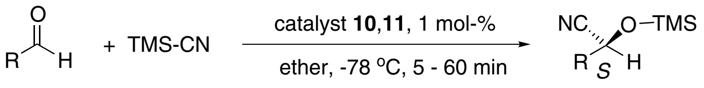
Scheme 6.7



mono-Li-salt
catalyst **10**



mono-Li-salt
catalyst **11**



R	Catalyst	Yield [%]	ee [%]	Ref.
Ph	**10**	96	56	52
Ph	**11**	98	86	53
4-Me-Ph	**10**	95	59	52
4-Me-Ph	**11**	96	93	53
3-Me-Ph	**10**	93	55	52
3-Me-Ph	**11**	88	97	53
3-MeO-Ph	**10**	89	52	52
3-MeO-Ph	**11**	96	77	53
4-*i*-Pr-Ph	**11**	99	82	53

Scheme 6.8

continuous "race" between enzymes, organocatalysts, and metal-complex-based methods. In the 1980s–1990s organocatalysis took a big step forward, because of the discovery of the Inoue catalyst. Unfortunately, and despite the extensive work of many excellent research groups in this field, the Inoue diketopiperazine catalysts still remain applicable – with synthetically useful enantioselection – for a relatively narrow range of aldehydes only. Aromatic aldehydes, preferably benzaldehyde derivatives with electron-donating substituents, are the "best" substrates, but even so not all substitution patterns are tolerated. The long sought-for generalization of the substrate spectrum has yet to be achieved. The situation is further complicated by the capricious conditions of heterogeneous catalysis and the auto-

induction phenomena involved. Nevertheless, cyanohydrins of quite a number of aromatic aldehydes have been prepared with >90% ee. A clear advantage of diketopiperazines is their ready availability from cheap starting materials and their stability. Very interesting recent and alternative developments are alkaloid-catalyzed carboxycyanation (using cyanoformates) and trimethylsilylcyanation (using TMS-CN) reported by Tiang and Deng. For these two transformations, α,α-disubstituted ketones and α-acetal ketones seem to be the best substrates, and enantiomeric excesses in the range 90–98% have been achieved for several substrates. Another intriguing catalytic process is trimethysilylcyanation using BINOLates and "salenates", discovered by Kagan and Holmes. It can be assumed that variations of the salens employed will further broaden the scope of the reaction.

6.2
Aldol Reactions

6.2.1
Intermolecular Aldol Reactions

6.2.1.1 Intermolecular Aldol Reaction With Formation of *One* Stereogenic Center

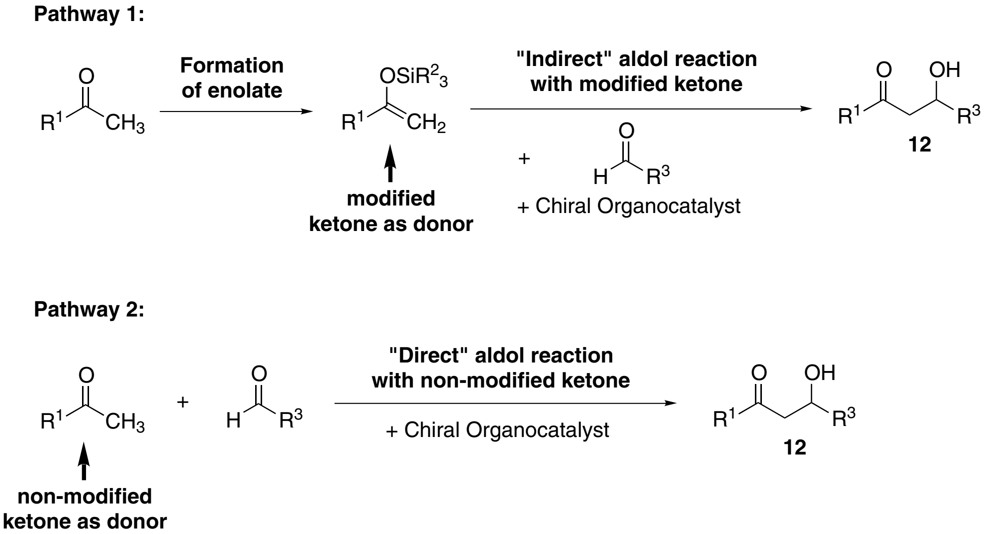
The asymmetric aldol reaction is one of the most important topics in modern catalytic synthesis [54]. The products, namely β-hydroxy carbonyl compounds, have a broad range of applications and play a key role in the production of pharmaceuticals [55]. Since the discovery of the catalytic asymmetric aldol reaction with enolsilanes by Mukaiyama et al. [56], steady improvements of the metal-catalyzed asymmetric aldol reaction have been made by many groups [57]. For this type of aldol reaction a series of chiral metal catalysts which act as Lewis acids activating the aldol acceptor have been shown to be quite efficient. It was recently shown by the Shibasaki group that the asymmetric metal-catalyzed aldol reaction can be also performed with unmodified ketones [57a]. During the last few years, several new concepts have been developed which are based on use of organocatalysts [58]. Enolates and unmodified ketones can be used as aldol donors.

In the text below organocatalytic asymmetric aldol reactions are classified into "indirect aldol reactions" and "direct aldol reactions". "Indirect aldol reactions" are syntheses which require a modified ketone as a starting material (Scheme 6.9, pathway 1). For example, enolates which are prepared in a previous step starting from the ketone are often used. Syntheses which allow the "direct" use of a ketone, in a non-activated form, as a nucleophile are defined as "direct aldol reaction" (Scheme 6.9, pathway 2).

"Indirect aldol reaction" using enolates

Aldol reactions using phosphoramides as organocatalyst

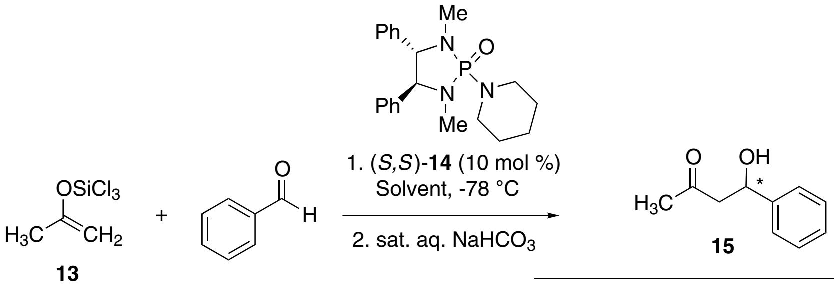
The concept In the first example of an organic base-catalyzed asymmetric intermolecular aldol reaction, Denmark et al. impressively demonstrated that the pres-



Scheme 6.9

ence of catalytic amounts of transition metals is not necessarily a prerequisite for successful asymmetric aldol reactions [59]. Originally developed for synthesis of aldol products with two stereogenic centers (Section 6.2.1.2) this method can be also efficiently used for products with one stereogenic center, in accordance with Scheme 6.10 [60–64].

Trichlorosilylenolates of type **13** were used as nucleophiles. Such enolates are highly activated ketone derivatives and react spontaneously with several aldehydes at room temperature. At −78 °C, however, the uncatalyzed reaction can be suppressed almost completely (formation of the undesired racemic aldol adduct is only 4%). Thus, at −78 °C and in the presence of the chiral organocatalyst **14** the acetone-derived enolate and benzaldehyde gave the desired adduct in high yield



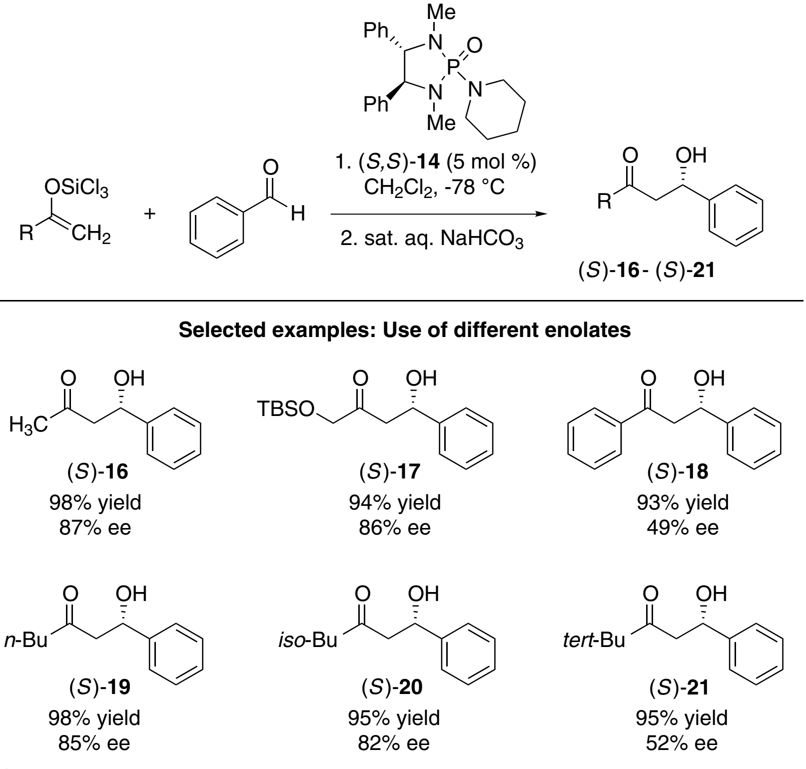
Solvent	Yield (%)	ee (%)
Dichloromethane	92	85 (*S*)
Propionitrile	88	79 (*R*)

Scheme 6.10

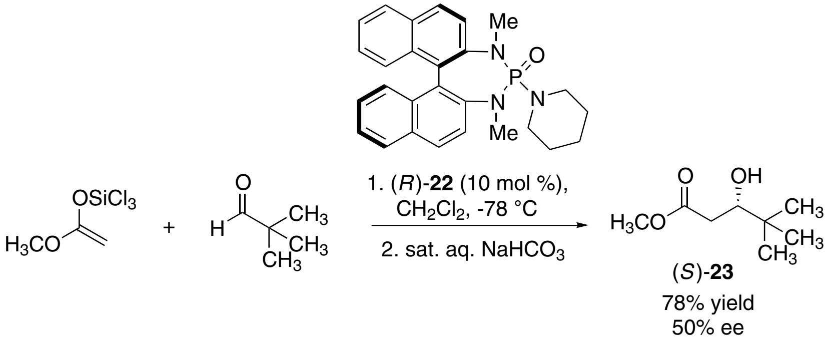
(92%) and with enantioselectivity of 85% ee [60]. Among a broad variety of chiral phosphoramide the molecule **14** turned out to be the preferred catalyst for this reaction. A significant solvent effect was also observed – the best yields (up to 92%) and enantioselectivity (up to 85% ee) were obtained by use of dichloromethane or propionitrile (Scheme 6.10) [60]. It is worthy of note, however, that the preferred enantiomers of **15** are opposite to each other for these solvents. Thus, with one type of enantiomerically pure catalyst both enantiomers of the desired aldol adduct can be produced enantioselectively simply by changing the solvent.

The substrate range – scope and limitations The reaction can be performed efficiently with a broad variety of ketone donors and aldehydes. Enantioselectivity, however, depends on the enolate structure (Scheme 6.11) [60, 61]. In general, enolates bearing larger, branched alkyl groups or a phenyl group result in lower enantioselectivity. The best results were obtained with enolates bearing a methyl substituent (product (*S*)-**16**, 87% ee) or a siloxymethyl substituent (product (*S*)-**17**, 86% ee).

Efforts have also been made to utilize ketone acetals bearing a trichlorosilyl group as an enolate donor (Scheme 6.12) [63a]. This reaction led to optically active *β*-hydroxy carboxylic acid esters (*S*)-**23** in good yields, although enantioselectivity remained modest only (ee values up to 50% ee when phosphoramide is used in



Scheme 6.11



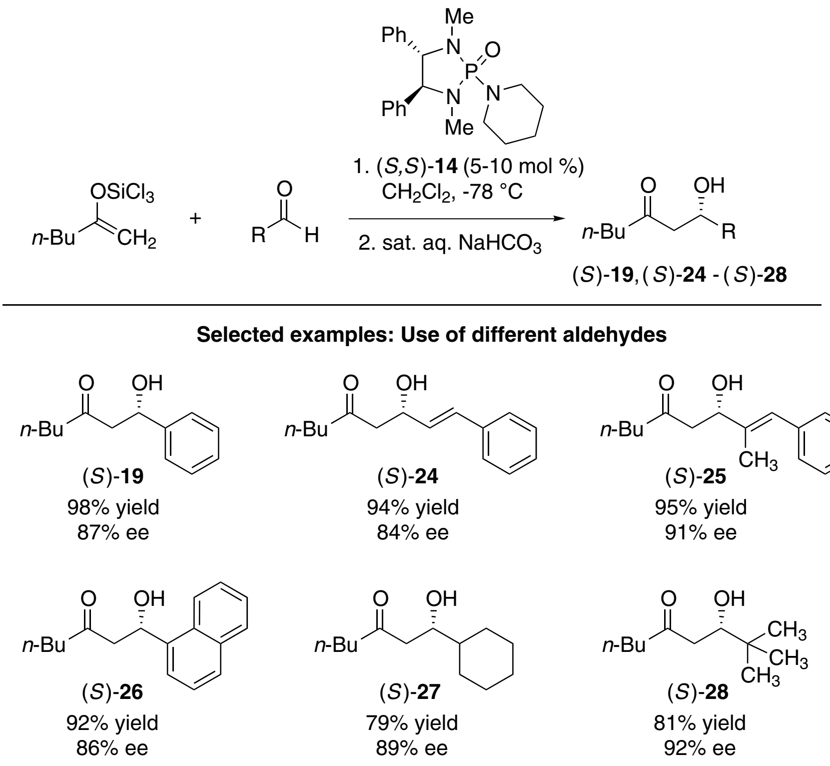
Scheme 6.12

catalytic amounts). A selected example of this type of synthesis is given in Scheme 6.12. For this reaction the phosphoramide of type **22** was found to be particularly useful [63a]. Use of other types of enolate in which one or more Cl atoms of the trichlorosilyl group are replaced by a proton or methyl or phenyl group did not give improved results, and usually led to reduced enantioselectivity [64]. This also shows that the phosphoramide-catalyzed aldol reaction is sensitive to the nature of the silyl group.

The Denmark method is synthetically very valuable, because a broad range of aldehyde acceptors can be used (Scheme 6.13) [60, 61]. Aromatic and α,β-unsaturated aldehydes react very rapidly in the presence of 5 mol% **14** as organocatalyst. The desired aldol products (*S*)-**19**, (*S*)-**24** to (*S*)-**26** were obtained in excellent yields of 92 to 98% and with high enantioselectivity (up to 91% ee).

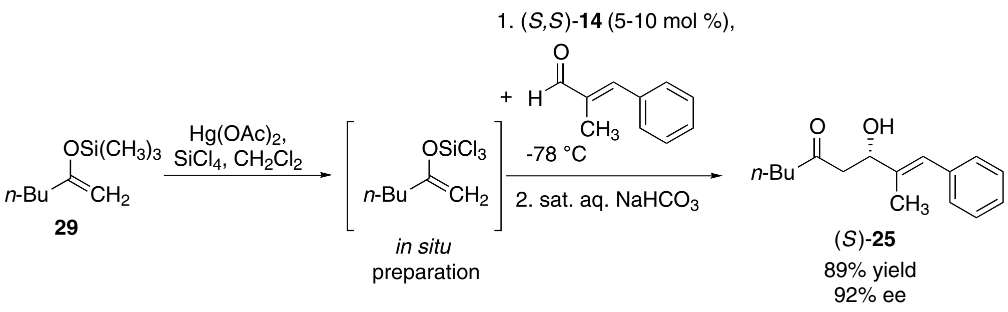
Branched aliphatic aldehydes are also tolerated, although a prolonged reaction time and larger amount of catalyst (10 mol%) is needed. For example, using pivaldehyde as substrate resulted in formation of the aldol adduct (*S*)-**28** in 81% yield and with an enantioselectivity of 92% ee. In contrast, unbranched aliphatic aldehydes did not afford the aldol adducts. An overview of the substrate range with regard to the aldehyde component is given in Scheme 6.13. Furthermore, the extension of this type of reaction towards the use of ketone substrates as acceptors has been reported by the Denmark group [63b]. In the presence of chiral bis *N*-oxides as organocatalysts, the desired β-hydroxy esters were obtained in up to 97% yield and with enantioselectivities of up to 86% ee.

Process development and optimization Detailed process development was conducted using synthesis of (*S*)-**16** as model reaction [60]. The preferred reaction temperature was −78 °C; lower temperatures, e.g. −90 °C, resulted in no improvement. With regard to the amount of catalyst, at least 5 mol% is required to obtain high enantioselectivity. Further increasing the amount of catalyst did not, however, result in sufficient improvement to justify use of an increased amount. From a practical standpoint the short reaction time (2 h for aromatic and α,β-unsaturated aldehydes) in combination with a high concentration of substrate (up to 0.5 mol L^{-1}) is attractive, and results in an excellent space–time yield of up to 856 g L^{-1} day^{-1}.



Scheme 6.13

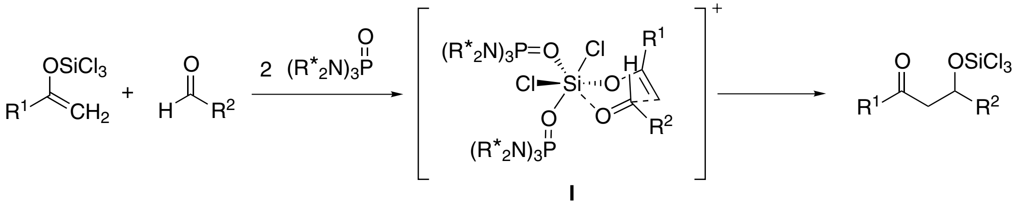
One practical limitation is the availability, storage, and handling of reactive trichlorosilyl enolates. Addressing this issue, Denmark et al. developed an interesting, more practical procedure entailing *in situ* preparation of those reactive species. Starting from a TMS enol ether **29**, *in situ* preparation of the trichlorosilyl enolate with tetrachlorosilane and mercury acetate, followed by subsequent asymmetric aldol reaction, gave the aldol product (*S*)-**25** in 89% yield and with 92% ee (Scheme 6.14).



Scheme 6.14

To achieve good yields excess of TMS enol ether **29** must be used. Although replacement of the required mercury salt would be desirable, this *in situ* preparation of the enolate and subsequent asymmetric aldol reaction is a practical method on a laboratory scale.

The mechanism A very detailed mechanistic study of this phosphoramide-catalyzed asymmetric aldol reaction was conducted by the Denmark group (see also Section 6.2.1.2) [59, 60]. Mechanistically, the chiral phosphoramide base seems to coordinate temporarily with the silicon atom of the trichlorosilyl enolates, in contrast with previously used chiral Lewis acids, e.g. oxazaborolidines, which interact with the aldehyde. It has been suggested that the hexacoordinate silicate species of type **I** is involved in stereoselection (Scheme 6.15). Thus, this cationic, diphosphoramide silyl enolate complex reacts through a chair-like transition structure.

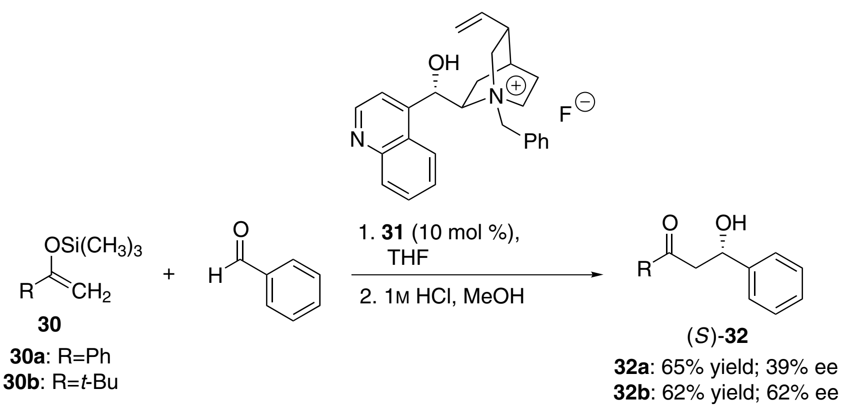


I
(chairlike
transition structure)

Scheme 6.15

In conclusion, the distinguishing characteristic of this type of phosphoramide-based "neutral" Lewis base catalysis is the potential of the reaction to proceed through an associative ("closed") transition structure. Thus pronounced diastereoselection results and control of the absolute configuration are possible. Currently, however, it seems difficult to explain the sense of induction based on transition state models [59, 60].

Aldol reactions using a quaternary chinchona alkaloid-based ammonium salt as organocatalyst Several quaternary ammonium salts derived from cinchona alkaloids have proven to be excellent organocatalysts for asymmetric nucleophilic substitutions, Michael reactions and other syntheses. As described in more detail in, e.g., Chapters 3 and 4, those salts act as chiral phase-transfer catalysts. It is, therefore, not surprising that catalysts of type **31** have been also applied in the asymmetric aldol reaction [65, 66]. The aldol reactions were performed with the aromatic enolate **30a** and benzaldehyde in the presence of ammonium fluoride salts derived from cinchonidine and cinchonine, respectively, as a phase-transfer catalyst (10 mol%). For example, in the presence of the cinchonine-derived catalyst **31** the desired product (*S*)-**32a** was formed in 65% yield (Scheme 6.16). The enantioselectivity, however, was low (39% ee) [65].

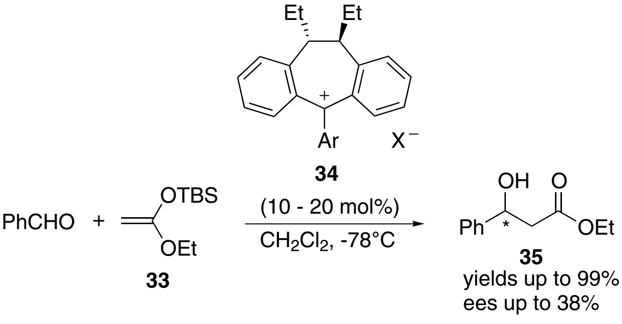


Scheme 6.16

Replacing **30a** by the bulky alkyl enolate **30b** as nucleophile led to an improved enantioselectivity (up to 62% ee) (Scheme 6.16). In both reactions the (*S*) enantiomer was preferably formed. The organocatalyst derived from cinchonine **31** was more efficient than that derived from cinchonidine [66].

Thus, in general, the aldol reaction proceeds in the presence of 10 mol% cinchona alkaloid salts of type **31**, although enantioselectivity does not exceed 62% ee [65, 66].

Aldol reactions using a carbocation as an organocatalyst An organocatalytic aldol reaction based on a different concept was developed by the Chen group. The chiral triarylcarbenium ion **34** was used as a novel non-metallic Lewis acid catalyst in a Mukaiyama-type aldol reaction which led to enantiomerically enriched aldol products (Scheme 6.17) [67]. Although non-chiral trityl salt-mediated catalytic aldol reactions had previously been reported by Mukaiyama and co-workers [68], the construction of a suitable chiral carbenium ion remained a challenge. Optically active salts of type **34** were synthesized as Lewis acids based on a reactive carbe-



Scheme 6.17

nium center. The yields of these highly moisture- and heat-sensitive materials of type **34** were in the range of 84–98%.

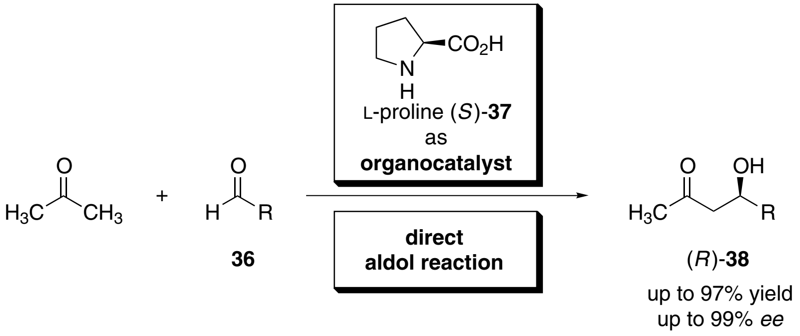
In the presence of catalytic amounts (10–20 mol%) of chiral trialkylcarbenium ion **34** the conversion of benzaldehyde and trimethylsilyl ketene acetal **33**, as model reaction, was investigated. The aldol adducts **35** were isolated in yields in the range 20 to 99% which were very dependent on conditions such as the counter ion of **34** or the reaction time. Enantioselectivity, however, never exceeded 40% ee, even when using sterically more bulky aromatic aldehydes. Gradual consumption of the catalytically active trityl ions and the significant intervention of undesired silyl catalysis, which lead to the unsatisfactory enantioselectivity, are still the main limitations of this method. Nevertheless, this first example of an asymmetric aldol reaction catalyzed by a chiral triarylcarbenium ion shows the high potential of this new type of chiral catalyst. In the future chiral carbenium ions such as **34** might be modified to increase their enantiodiscriminating potential, and chiral trityl salts will surely be of interest for other catalytic processes also.

"Direct aldol reaction" using unmodified ketones

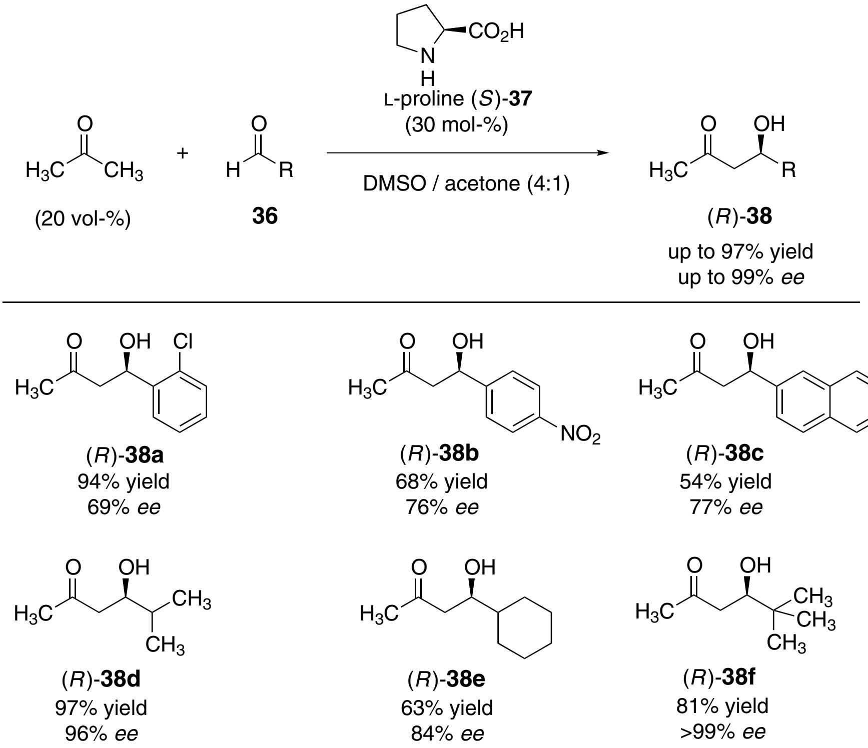
Aldol reactions using L-proline as organocatalyst

The concept The possibility of using a simple organic molecule from the "chiral pool" to act like an enzyme for the catalytic intermolecular aldol reaction has recently been reported by the List and Barbas groups [69–71]. L-proline, (*S*)-**37**, was chosen as the simple unmodified catalytic molecule from the "chiral pool". The proline-catalyzed reaction of acetone with an aldehyde, **36**, at room temperature resulted in the formation of the desired aldol products **38** in satisfactory to very good yields and with enantioselectivity up to >99% ee (Scheme 6.18) [69, 70a].

It is worth noting that, in a similar manner to enzymatic conversions with type I or II aldolases, a "direct" asymmetric aldol reaction was achieved when L-proline was used as catalyst. Accordingly, the use of enol derivatives of the ketone component is not necessary, i.e. ketones (acting as donors) can be used *directly* without previous modification [72]. So far, most asymmetric catalytic aldol reactions with



Scheme 6.18



Scheme 6.19

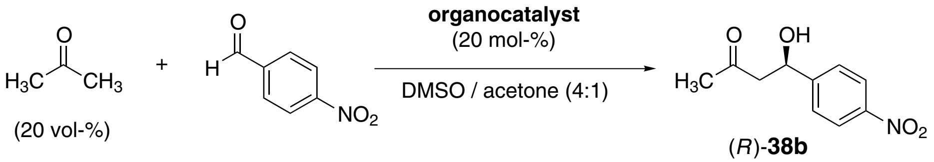
synthetic catalysts require use of enol derivatives [54, 56, 57]. The first direct catalytic asymmetric aldol reaction in the presence of a chiral heterobimetallic catalyst has recently been reported by the Shibasaki group [74, 75].

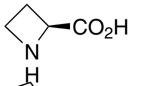
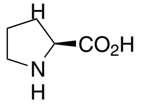
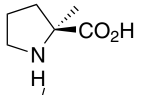
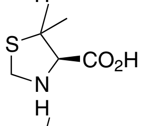
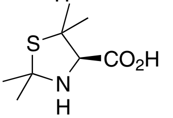
The substrate range: scope and limitations Promising prospects for synthetic applications of the proline-catalyzed aldol reaction in the future were opened up by experimental studies of the range of substrates by the List [69, 70a, 73] and Barbas [71] groups. The reaction proceeds well when aromatic aldehydes are used as starting materials – enantioselectivity is 60 to 77% ee and yields are up to 94% (Scheme 6.19) [69, 70]. The direct L-proline-catalyzed aldol reaction proceeds very efficiently when isobutyraldehyde is used as substrate – the product, (*R*)-**38d**, has been obtained in very good yield (97%) and with high enantioselectivity (96% ee).

Cyclohexyl carbaldehyde is also a good substrate [70a, 71]. Tertiary aldehydes, e.g. pivaldehyde, are excellent substrates, furnishing the aldol products, e.g. (*R*)-**38f**, with >99% ee and in high yield [70a]. Aliphatic α-unsubstituted aldehydes, e.g. pentanal, which usually undergo self-aldolization, can also yield optically active cross-aldol products [71, 73]. A prerequisite for efficient reaction is, however, that the reaction is conducted in neat acetone. Thus, a yield of 75% with 73% ee was achieved in the reaction of pentanal as acceptor and acetone as donor [71].

Despite the broad variety of aldehydes as suitable aldol acceptors the range of donors has remained narrow. Whereas acetone is an excellent nucleophile, a variety of other donors, e.g. acetophenone, 3-pentanone, acetylcyclohexane, and isopropyl methyl ketone did not yield significant amounts of the desired aldol products [70a, 71].

The Barbas group has reported the suitability of other heterocyclic α-amino acids, in particular 5,5-dimethyl thiazolidinium-4-carboxylate (DMTC, (*S*)-**41**), hydroxyproline, and derivatives thereof, as efficient organocatalysts [71]. In general, for a broad range of substrates catalytic performance similar to that of the efficient catalyst L-proline was observed for DMTC, although enantioselectivity was higher for some substrates [71]. In contrast, non-cyclic α-amino acids have not been found to be suitable catalysts for this type of reaction. An overview of the catalytic properties of selected proline-related, cyclic amino acids in a model reaction is shown in Scheme 6.20. A proline-derived tetrazole catalyst turned out to be highly efficient for the aldol reaction of various ketones with chloral [76a]. This has been demonstrated very recently by Saito and Yamamoto et al. achieving excellent enantioselectivities of up to 97% ee when applying (2*S*)-tetrazol-5-ylpyrrolidine as an organocatalyst (10 mol%) [76a]. Notably, stoichiometric amount of water accelerates the reaction. Furthermore, the Arvidsson group reported successful applications of



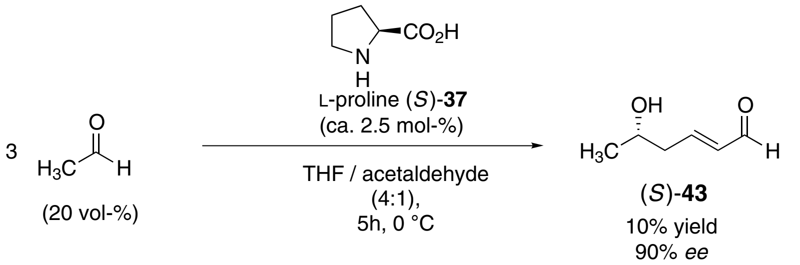
Type of organocatalyst		yield [%]	ee [%]
	(*S*)-**39**	55	40
	(*S*)-**37**	68	76
	(*S*)-**40**	26	61
	(*S*)-**41** (DMTC)	66	86
	(*S*)-**42**	<5	n.d.

Scheme 6.20

this tetrazole organocatalyst in the direct aldol reaction of various aldehydes with acetone very recently [76b]. The Berkessel group developed proline-derived *N*-sulfonylcarboxamides as easily accessible and highly efficient organocatalysts for the direct aldol reaction very recently [76c]. Compared to L-proline, significantly improved reactivities and enantioselectivities (of up to 98% ee) were obtained at low catalytic amounts of 5–10 mol%. In addition, variation of the sulfonamide part of these organocatalysts represents an option for substrate-specific fine-tuning of the catalyst.

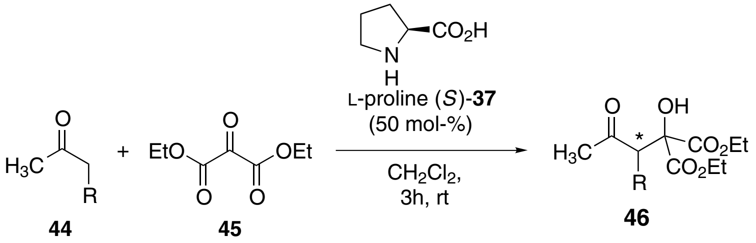
The List group demonstrated that *N*-terminal prolyl peptides also can efficiently catalyze the aldol reaction [76d]. The best result was obtained by use of the dipeptide Pro–Ser, which enabled formation of the aldol adduct between acetone and *p*-nitrobenzaldehyde in 87% yield and with 77% ee (compared with 68% yield and 76% ee when using proline as a catalyst under the same conditions). These promising results with *N*-terminal prolyl peptides are particularly worthy of note when it is considered that use of proline amide itself resulted in low enantioselectivity (with only 20% ee for the aldol adduct between acetone and *p*-nitrobenzaldehyde).

Extensions of the proline-catalyzed aldol reaction Recently interesting extensions of the enantioselective proline-catalyzed aldol reaction have been reported. An enantioselective proline-catalyzed self-aldolization of acetaldehyde was observed by Barbas and co-workers (Scheme 6.21) [77]. Starting from acetaldehyde, the valuable building block 5-hydroxy-(2*E*)-hexenal, (*S*)-**43**, was obtained as a product with up to 90% ee, although the yield did not exceed 13%, irrespective of the reaction conditions. This reaction requires a small amount catalyst only (ca. 2.5 mol%).



Scheme 6.21

Another interesting extension of the proline-catalyzed aldol reaction was recently reported by the Jørgensen group (Scheme 6.22), who used keto malonates as acceptors and α-substituted acetone derivatives as donors [78]. In contrast with the "classic" proline-catalyzed reaction discussed above, in this reaction the stereogenic center is formed at the nucleophilic carbon atom of the donor. The resulting products of type **46** are formed in good yields, from 88% to 94%, and with enantioselectivity between 84 and 90% ee (Scheme 6.22). The reactions were performed with a catalytic amount of 50 mol% [78].



46	R	Yield [%]	ee [%]
a	Me	90	90
b	Et	91	85
c	*i*-Pr	88	85
d	$CH_2CH{=}CH_2$	94	88
e	*n*-Hex	91	84

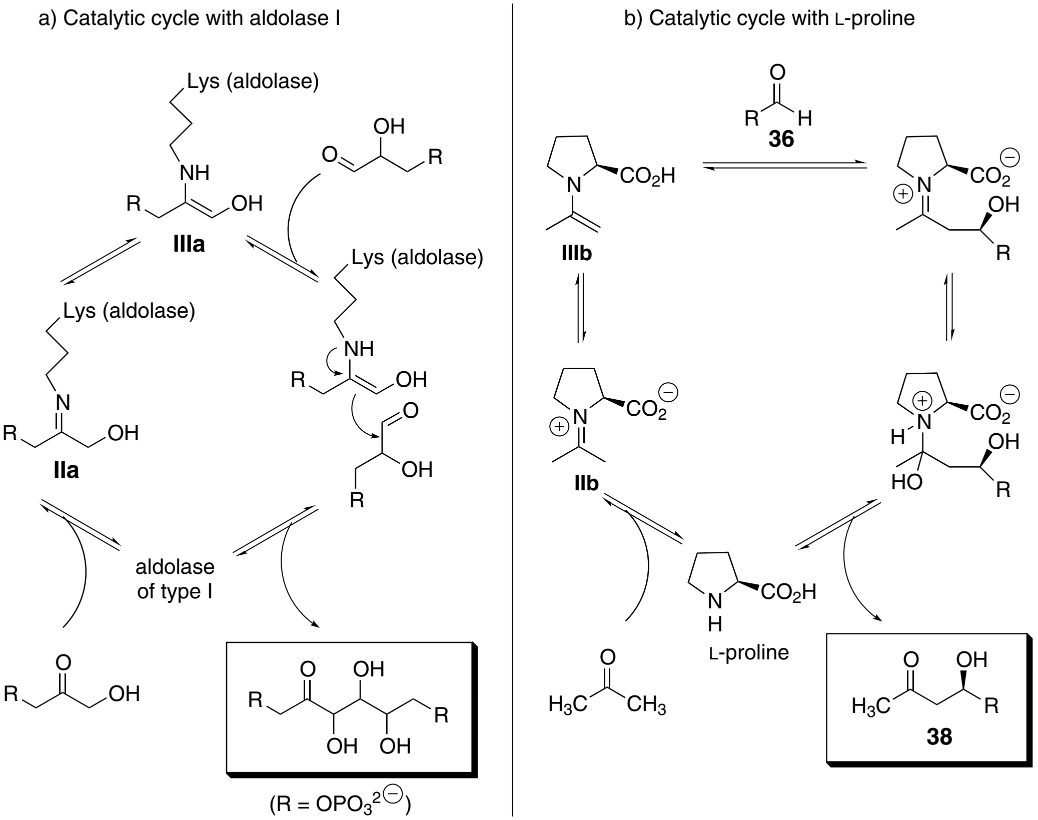
Scheme 6.22

Process development and optimization A disadvantage is the large excess of the ketone component usually required (although in one model reaction it was shown that stoichiometric amounts can also be used; Section 6.2.1.2). In addition, a further reduction of the amount of catalyst required to 20–30 mol% would be desirable for an efficient catalytic process.

Several investigations addressing these issues were performed in process-optimization experiments [71]. With regard to efficient recovery and re-use of the catalyst, use of chloroform is suitable, because of the insolubility of L-proline. Although the ee obtained was somewhat lower (61% ee for (*R*)-**38b** in $CHCl_3$ compared with 76% ee in DMSO), the organocatalyst was quantitatively recovered by simple filtration and re-use of the catalyst indicated there was no loss of activity. As an alternative method, immobilization of L-proline on a silica gel column was studied but resulted in less satisfactory results [71].

The Kotsuki group investigated the effect of high-pressure conditions on the direct proline-catalyzed aldol reaction [79a], a process which, interestingly, does not require use of DMSO as co-solvent. Use of high-pressure conditions led to suppression of the formation of undesired dehydrated by-product and enhancement of the yield. Study of the substrate range with a range of aldehydes and ketones revealed that enantioselectivity was usually comparable with that obtained from experiments at atmospheric pressure. Additionally, proline catalyzed aldol reactions in ionic liquids, preferably 1-butyl-3-methylimidazolium hexafluorophosphate, have been successfully carried out [79b,c].

The mechanism: similarities to enzymatic processes In principle, L-proline acts as an enzyme mimic of type I metal-free aldolases. Similar to this enzyme, L-proline catalyzes the direct aldol reaction according to an enamine mechanism. Thus, for the first time a mimic of type I aldolases has been found. The close similarity of

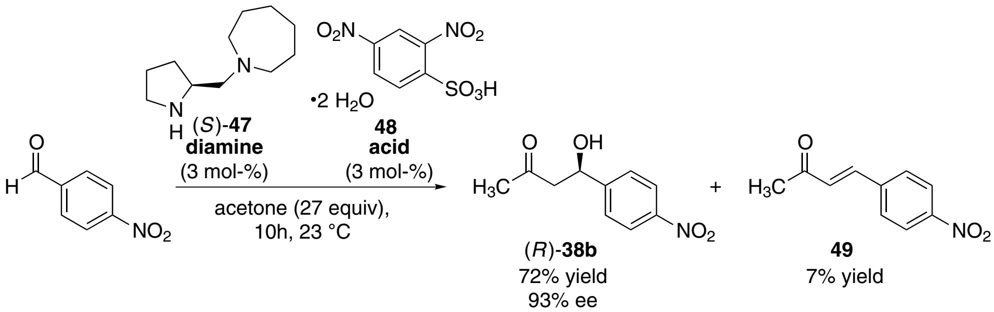


Scheme 6.23 (from Ref. [80])

the mechanisms of reaction of type I aldolases [54d] and L-proline [69] is shown by graphical comparison of both reaction cycles in Scheme 6.23 [80]. In both mechanisms formation of the enamines **IIIa** and **IIIb**, respectively, is the initial step. These reactions start from the corresponding ketone and the amino functionality of the enzyme or L-proline. Conversion of the enamine intermediates **IIIa** and **IIIb**, respectively, with an aldehyde, and subsequent release of the catalytic system (type I aldolase or L-proline) furnishes the aldol product.

The catalytic cycles are, however, different in the reaction sequence for formation of the enamines which are key intermediates in these aldol reactions. With the type I aldolase a primary amino function of the enzyme is used for direct formation of a neutral imine (**IIa**) whereas starting from L-proline enamine synthesis proceeds *via* a positive iminium system (**IIb**) (Scheme 6.23). In this respect, investigations by List et al. on the dependence of the catalytic potential on the type of amino acid are of particular interest. In these studies it has been shown that for catalytic activity the presence of a pyrrolidine ring (in L-proline (*S*)-**37**) and the carboxylic acid group is required [69].

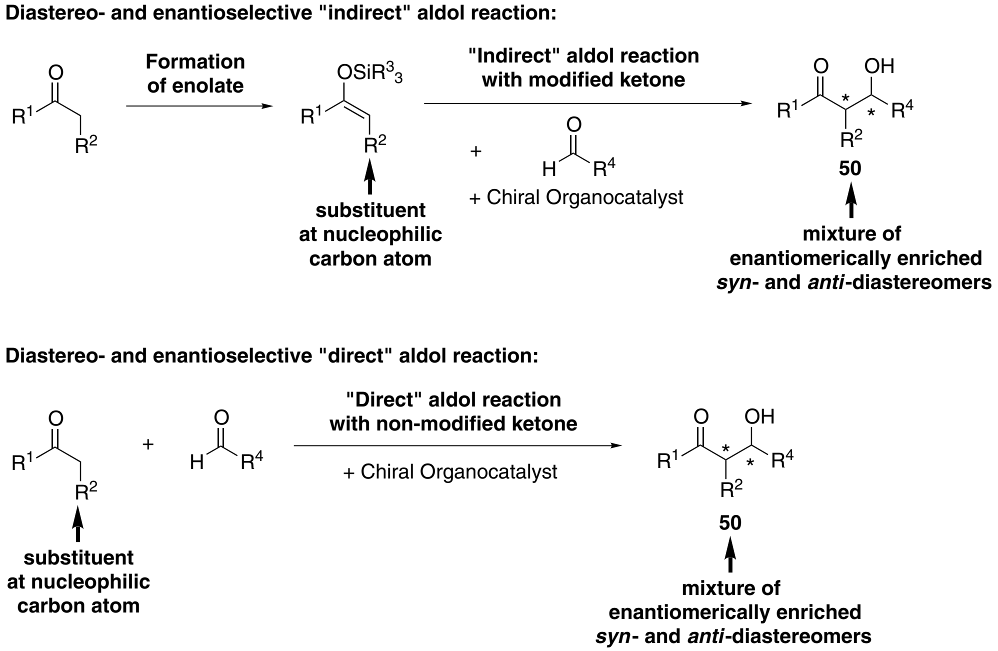
Aldol reactions using a diamine as organocatalyst The Yamamoto group showed organocatalytic asymmetric aldol reaction can be also performed successfully with optically active diamines derived from L-proline [81]. A detailed screening study of several libraries revealed that selected combinations of a diamine and a protonic acid are suitable catalysts leading to enantioselectivity up to 93% ee [81a]. As substrates acetone was used as a donor in combination with aromatic or aliphatic aldehydes. The ratio of the chiral diamine and the (non-chiral) acid is important. The most suitable diamine-to-acid ratio was found to be 1:1. For *p*-nitrobenzaldehyde and acetone several type of acid and diamine were screened using a small amount of catalyst (3 mol%). Under these conditions the best result was obtained with the optically active diamine (*S*)-**47** and the acid **48**, furnishing the desired product (*R*)-**38b** in 72% yield and with 93% ee (Scheme 6.24) [81a]. In contrast, this organocatalyst (*S*)-**47** was less suitable for use of benzaldehyde as a substrate (13% yield; 91% ee; 25% yield for the side product **49**). For benzaldehyde and cyclohexyl carbaldehyde as substrates related organocatalysts based on other diamines were found to be efficient. Thus, by means of organocatalyst screening using a diamine library an optimized, substrate-specific organocatalyst was found for each type of substrate. It was also found, however, that dehydration of the aldol product is often a critical side reaction, with yields in the range 4 to 57%.



Scheme 6.24

Conclusion

Without any doubt one can regard the asymmetric synthesis of aldol products with one stereogenic center as one of most advanced types of synthesis in the field of organocatalysis. The desired aldol products can be obtained in high yields and with good to excellent enantioselectivity. In addition, conceptually completely different organocatalytic approaches have been developed which entail use of organic Lewis bases phase-transfer catalysts, carbocations and amino acids (and derivatives thereof), respectively, as organocatalysts. The Denmark method using chiral phosphoramides as Lewis base catalysts and the List and Barbas approach applying proline (or derivatives thereof) as a simple but efficient organocatalyst are surely among the most efficient and general asymmetric catalytic aldol reactions yet discovered. In summary, organocatalytic aldol reactions provide the organic chemist



Scheme 6.25

with a valuable and versatile tool for efficient preparation of optically active aldol adducts.

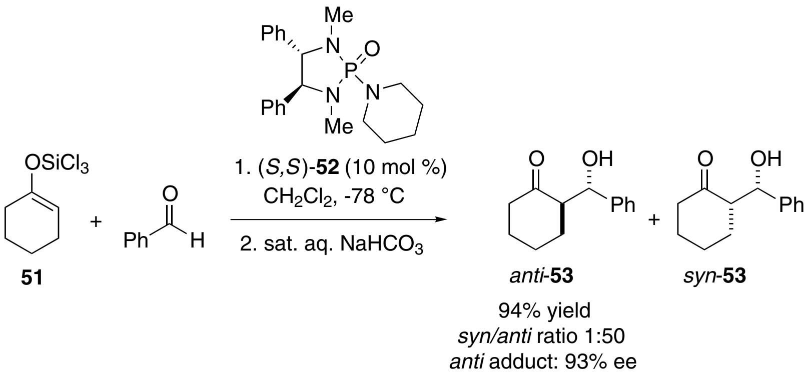
6.2.1.2 Intermolecular Aldol Reaction with Formation of *Two* Stereogenic Centers

The asymmetric aldol reaction can also be performed as an enantio- and diastereoselective reaction forming molecules of type **50** with two stereogenic centers. The principle of this reaction is shown in Scheme 6.25.

Several organic molecules have been found to catalyze this process efficiently. As described in Section 6.2.1.1, the syntheses can be performed as "indirect" or "direct" aldol reactions. Thus, as nucleophiles, ketones were applied directly or enolates can be used as starting materials.

"Indirect aldol reaction" using enolates

Aldol reactions using phosphoramides as organocatalysts The organic base-catalyzed asymmetric intermolecular aldol reaction with ketone-derived donors can be successfully applied to the construction of aldol products with two stereogenic centers [82–86]. Trichlorosilyl enolates of type **51** have been used as nucleophiles. Such enolates are strongly activated ketone derivatives and react spontaneously with several aldehydes at −80 °C. A first important result was that in the aldol reaction of **51** catalytic amounts of HMPA led to acceleration of the rate of reaction. After screening several optically active phosphoramides as catalysts in a model reaction the aldol product *anti*-**53** was obtained with a diastereomeric



Scheme 6.26

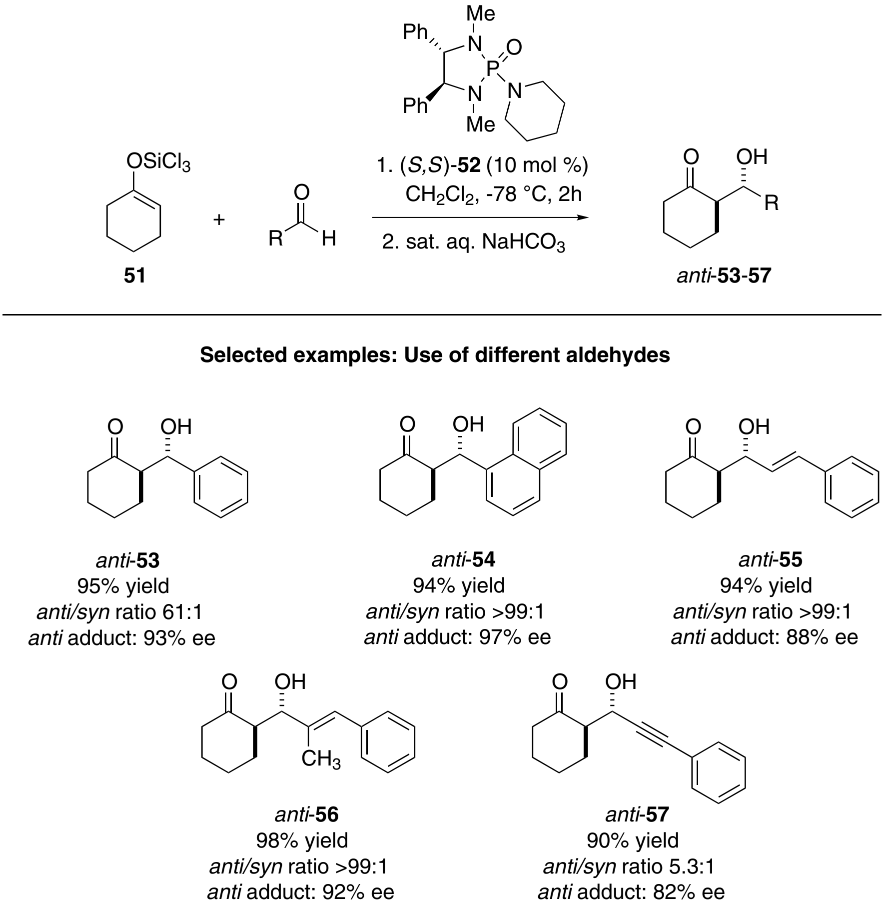
ratio, d.r., (anti/syn) of 50:1, and an enantioselectivity of 93% ee (for the anti enantiomer) in a high yield (94%) under non-optimized conditions when using 10 mol% (*S*,*S*)-**52** (Scheme 6.26) [84].

It should be noted that in the absence of the organocatalyst the *E* enolate affords mainly the syn adduct (syn/anti ratio 49:1, 92% yield, reaction temperature 0 °C [82, 84]) whereas in the presence of (*S*,*S*)-**52** by dramatic reversal in diastereoselectivity the anti-aldol product *anti*-**53** is preferentially formed (anti/syn ratio 50:1; anti 93% ee) [84]. Other types of chiral phosphoramide, e.g. based on optically active 1,2-cyclohexyldiamine, had less satisfactory catalytic properties.

Several reaction conditions, e.g. the solvent and the rate of mixing, have a significant effect on the reaction [84]. Under optimized conditions the reaction is performed with an amount of catalyst of only 2 mol% (*S*,*S*)-**52** in the presence of dichloromethane as solvent. A further prerequisite for efficient reaction is, however, dropwise addition of the aldehyde component. For example, a yield of 91%, high anti/syn diastereoselectivity of 28:1, and 92% ee for the anti product *anti*-**53** was obtained under such conditions when using benzaldehyde and the trichlorosilyl ether derived from cyclohexenone as substrates. On rapid addition of the aldehyde, however, 10 mol% catalyst was required for comparable selectivity.

The range of suitable aldehydes was investigated using the organocatalyst (*S*,*S*)-**52** and the cyclohexanone-derived trichlorosilyl enolate **51** as prototypical (*E*)-enolate (Scheme 6.27) [84]. Irrespective of the aldehyde used high yields of 90 to 98% were obtained. The diastereoselectivity was excellent for aromatic and unsaturated aldehydes, with anti/syn ratios between 61:1 and >99:1. Enantioselectivity for the anti enantiomer was high, between 88 and 97% ee. Selected examples are given in Scheme 6.27. The acetylenic aldehyde led to somewhat lower diastereo- and enantioselectivity (anti/syn ratio 5.3:1; anti-adduct 82% ee).

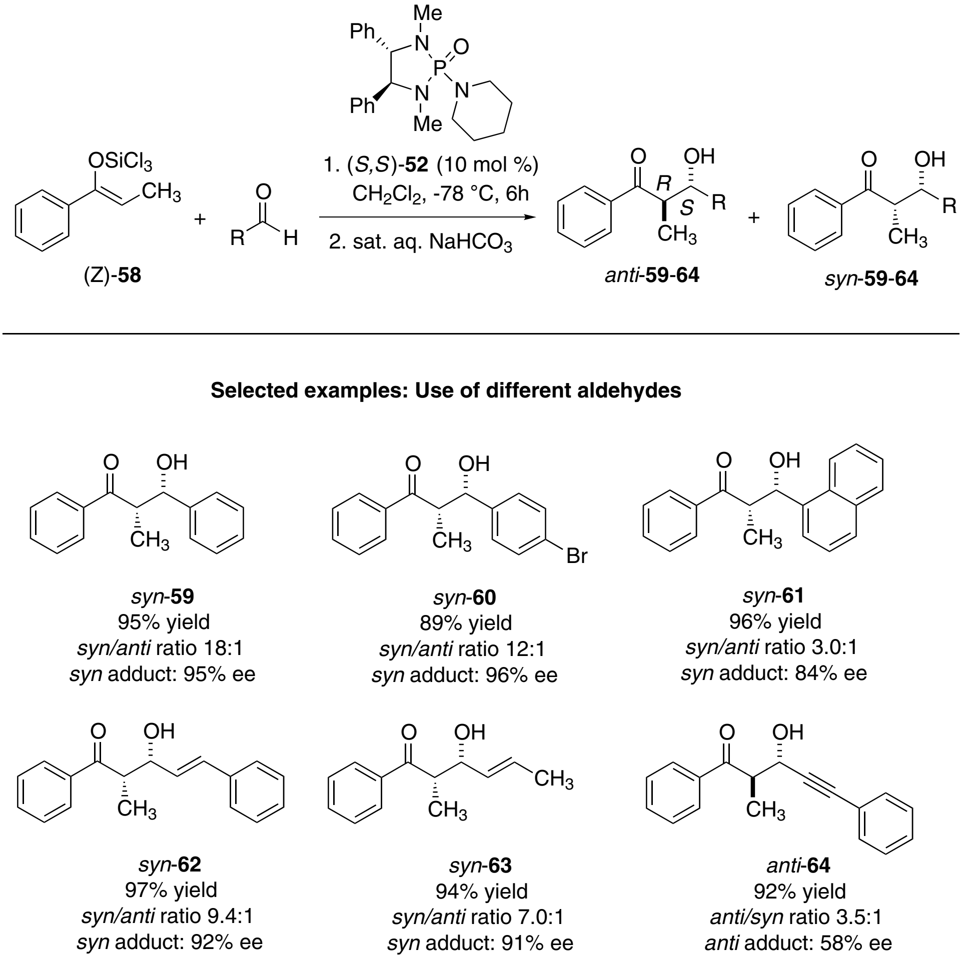
The reaction also proceeds efficiently with (*Z*)-enolates, as has been demonstrated with the trichlorosilyl enolate derived from propiophenone, (*Z*)-**58** (Scheme 6.28). With aromatic and olefinic aldehydes the syn products *syn*-**59**–**63** were formed as preferred diastereomers in high yields (89 to 97%) and with moderate to high syn/anti ratio (3.0:1 to 18:1). Enantioselectivity for the preferred syn diaster-



Scheme 6.27

eomers *syn*-**59**–**63** were high (from 84 to 96% ee). For the corresponding reaction using the acetylenic aldehyde, however, anti-diastereoselectivity (syn/anti 1:3.5) was observed and enantioselectivity of 58% ee and 10% ee, respectively, for both enantiomers *syn*-**64** and *trans*-**64** [84].

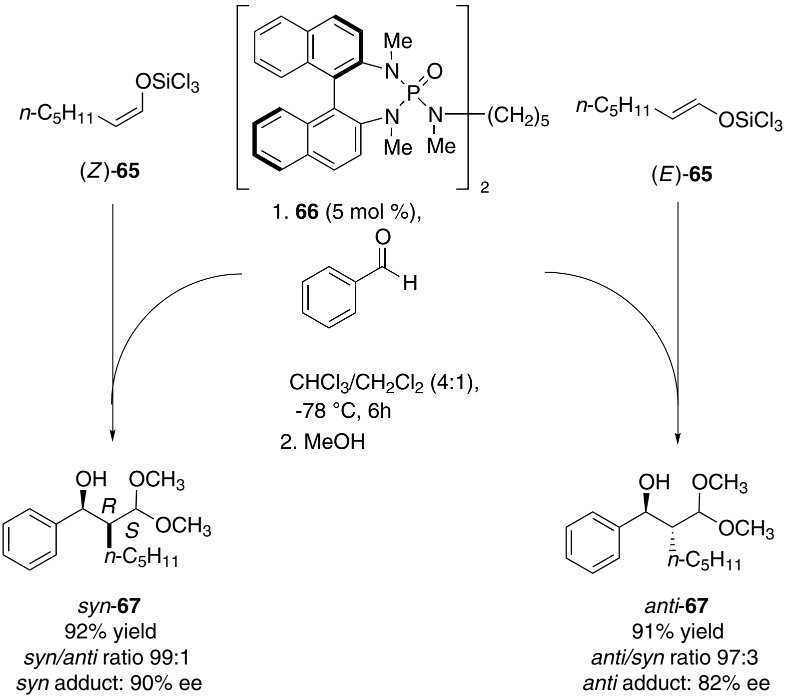
The Denmark phosphoramide organocatalyst has recently been applied in the first catalytic, diastereoselective, and enantioselective crossed-aldol reaction of aldehydes [86]. It is worthy of note that such controlled stereoselective self-condensation of aldehydes has previously found no general application, because of many side-reactions, e.g. polyaldolization, and dehydration of the products. Several previously developed solutions have limitations. In a first step the Denmark group developed a procedure for generation of stereodefined trichlorosilyl enolates of aldehydes with high geometrical purity. Use of these geometrically pure (*Z*) and



Scheme 6.28

(E) compounds of types (Z)-**65** and (E)-**65** in reactions with benzaldehyde, with phosphoramides as catalysts, furnished the aldol products (as their dimethyl acetal derivatives, for reasons of stability) in high yield and diastereoselectivity. Enantioselectivity, however, was low when monomeric phosphoramide was used as catalyst. A breakthrough with regard to enantioselectivity was achieved when monomeric catalysts were replaced by the dimeric phosphoramide **66**. Interestingly, the length of the alkyl linker plays a crucial role in enantioselectivity, the best results being obtained when $n = 5$. The products were obtained with excellent yields and diastereoselectivity accompanied (usually) by good to high enantioselectivity. A selected example is shown in Scheme 6.29.

The phosphoramide-catalyzed cross-aldol reaction tolerates a broad variety of

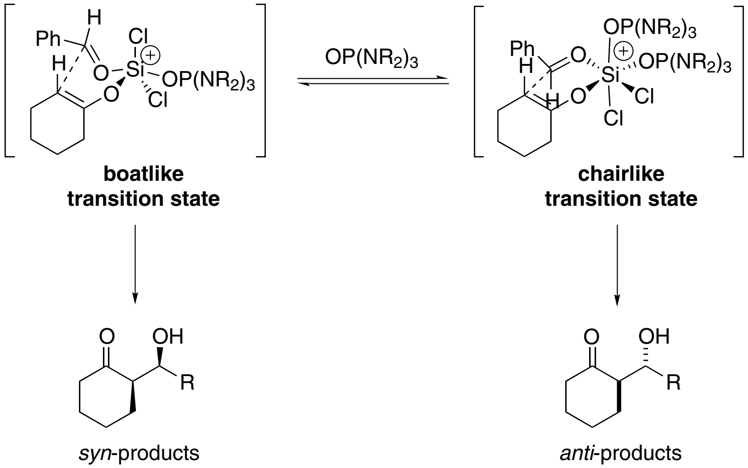


Scheme 6.29

aldehydes [86]. Use of enolates of type (*Z*)-**65** and (*E*)-**65** with aromatic aldehydes as acceptors gave the desired cross-aldol products of type **67** in yields of 91 to 97% with diastereomeric ratios of 97:3 to 99:1. A representative example is given in Scheme 6.29. It is worthy of note that use of (*Z*)-enolates usually gave the syn products preferably whereas use of (*E*)-enolates furnished the anti products. The enantioselectivity was variable with ee values in the range 53 to 90% ee. In addition to aromatic aldehydes, α,β-unsaturated aldehydes and acetylenic and aliphatic aldehydes were also used successfully. Yields and diastereoselectivity were usually high for those substrates, also, although enantioselectivity was usually somewhat lower than for aromatic aldehydes.

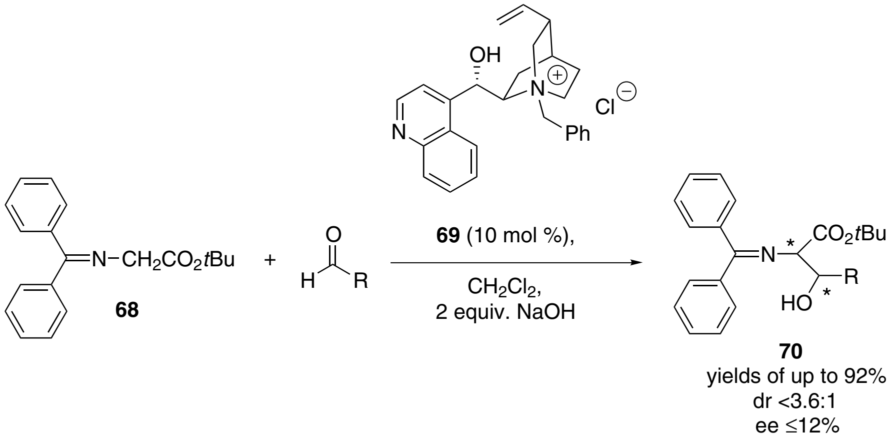
The basic principles of the mechanism of this Lewis-base-catalyzed aldol reaction have already been described in Section 6.2.1.1. With regard to the course of the enantio- and diastereoselective formation of aldol adducts with two stereogenic centers, it is proposed that synthesis of anti-products proceeds *via* a chair-like transition structure. A distinctive feature of the cationic transition state complex is a hexacoordinated silicon atom bearing two chiral phosphoramide molecules as ligands (Scheme 6.30).

In contrast, syn products are formed through a boat-like transition state, also involving a cationic silicon complex. In this complex, however, the silicon atom is pentacoordinated and one phosphoramide only is bound to the silicon atom.



Scheme 6.30

Aldol reactions using quaternary ammonium salts as organocatalysts Alkaloid-based quaternary ammonium salts are suitable organocatalysts for diastereo- and enantioselective aldol reactions furnishing optically active *β*-hydroxy-*α*-amino acids. As starting material, *tert*-butylglycinate–benzophenone Schiff base **68** turned out to be less preferred compared with a silylated derivative thereof for this reaction. In an early study Miller et al. showed the "proof of principle" for this reaction using chloride salts of cinchona alkaloids (an example is given in Scheme 6.31) [87]. A long alkyl chain on the aldehyde was found to be beneficial. Aromatic aldehydes were also tolerated. The yields of these substrates were medium to good, between 46 and 92%, whereas diastereomeric ratio was medium to low, the best d.r. being 3.5:1. The enantioselectivity of the diastereomeric products was very low and not

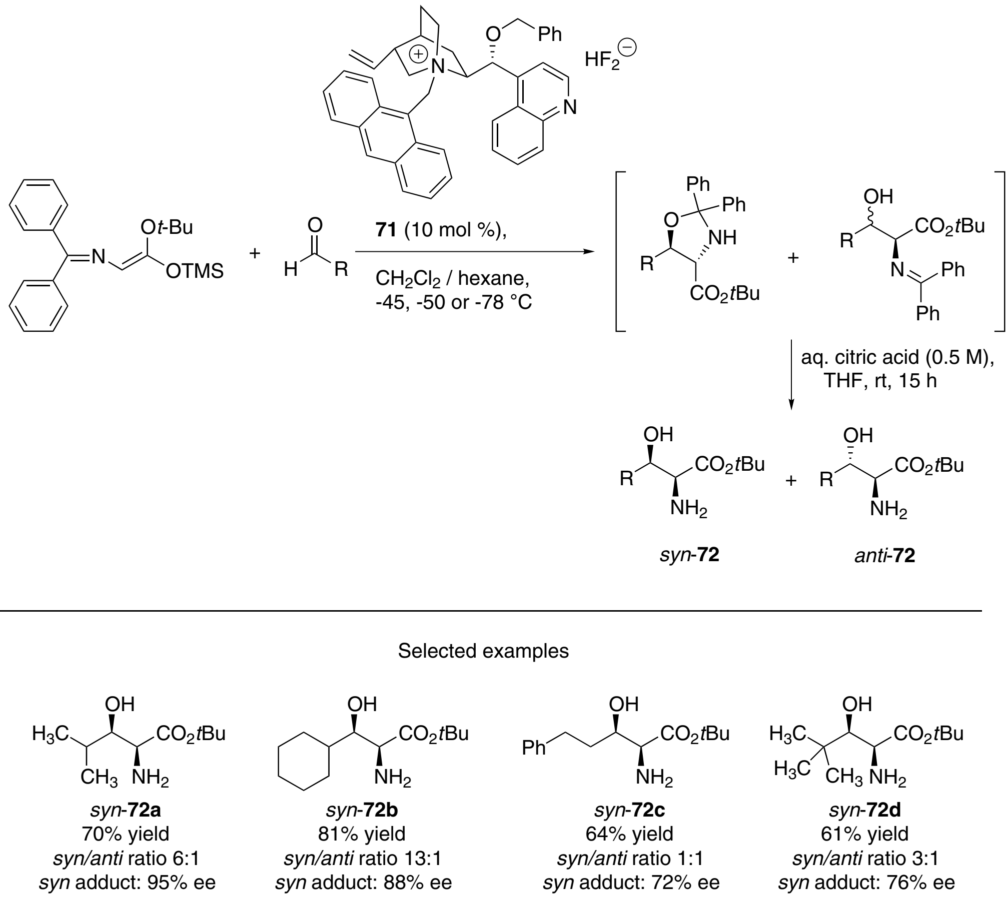


Scheme 6.31

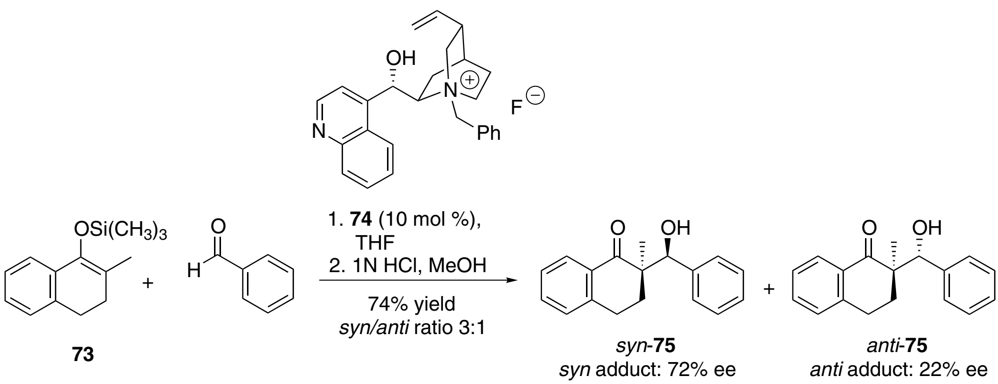
sufficient for practical asymmetric syntheses – the highest enantioselectivity was 12% ee.

A breakthrough leading to high enantioselectivity was achieved by the Corey group, who used the chinchonidine-derived organocatalyst they had previously developed for, e.g., enantioselective Michael addition (Section 4.1) [88]. On use of a catalytic amount (10 mol%) and the trimethylsilyl enol ether derivative of *tert*-butylglycinate–benzophenone Schiff base as aldol donor the reaction proceeds with a broad variety of aldehydes (Scheme 6.32). In the first step an isomeric mixture of oxazolidine and β-hydroxy-α-amino acid ester Schiff base with benzophenone is formed; this is subsequently cleaved by treatment with citric acid, with formation of the desired products **72**. Most interestingly, good to excellent enantioselectivity of up to 95% ee was usually obtained. Diastereoselectivity, however, varied substantially – syn/anti ratios were from 1:1 to 13:1. Yields were in the range 48 to 81%. Selected examples are given in Scheme 6.32.

Another catalytic application of chiral quaternary ammonium salts is their use



Scheme 6.32



Scheme 6.33

in the diastereo- and enantioselective synthesis of α-dialkylated β-hydroxy ketones of type **75** [89]. The Shioiri group found that reaction of the trimethylsilyl enolate nucleophile **73** and benzaldehyde proceeds with medium to good diastereoselectivity (d.r. ratio up to 7.3:1). Yields are in the range 63 to 74%. Enantioselectivity was usually higher for the syn diastereomer, with ee values up to 72% ee. A representative example is shown in Scheme 6.33.

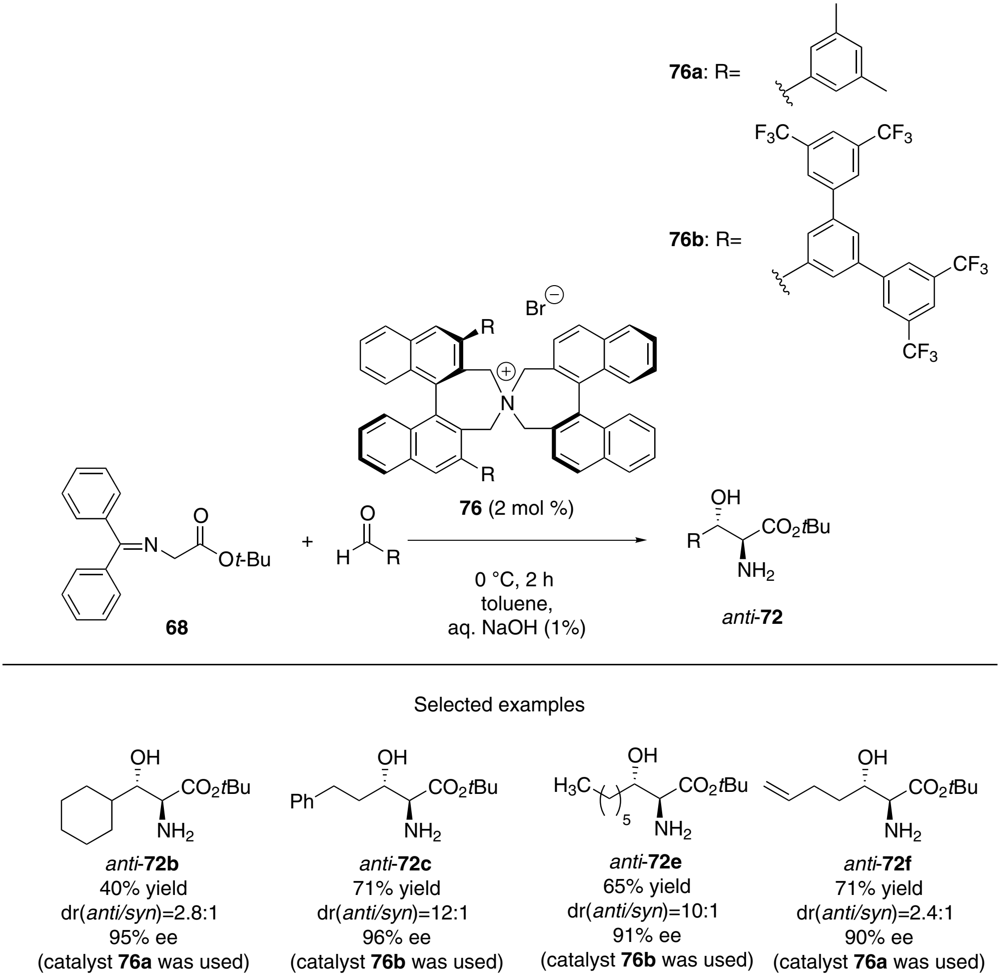
A catalytic amount (12 mol%) of *N*-benzylchinchonium fluoride salt **74** was used as organocatalyst. The solvent has a crucial effect on the efficiency of the reaction. It was observed that THF gave the best results and that the enantioselectivity dropped substantially when a polar solvent such as DMF or acetonitrile was added. If the reaction was performed in ether or toluene an aldol product was not obtained.

"Direct aldol reaction" using glycinates

A new class of chiral quaternary ammonium salt organocatalyst has recently been developed by Maruoka and co-workers, and successfully applied in enantioselective alkylations [90]. The Maruoka group recently also demonstrated that these structurally rigid spiro ammonium salts of, e.g., type **76**, are also suitable catalysts for the diastereo- and enantioselective aldol reaction of glycinate **68** with aldehydes [91]. In the presence of the C_2-symmetric compounds **76a** or **76b** as organocatalysts formation of the desired β-hydroxy α-amino acid derivatives *anti*-**72** proceeds with high diastereoselectivity and enantioselectivity. The asymmetric aldol reaction can be performed by direct use of the glycine Schiff base as donor without previous modification. This direct diastereo- and enantioselective aldol reaction has been successfully performed with a broad range of aldehyde substrates. Selected examples are shown in Scheme 6.34. For example, a high diastereomeric ratio of d.r. (anti/syn) = 12:1 and high enantioselectivity of 96% ee were observed for formation of *anti*-**72c**.

"Direct aldol reaction" using unmodified ketones and aldehydes

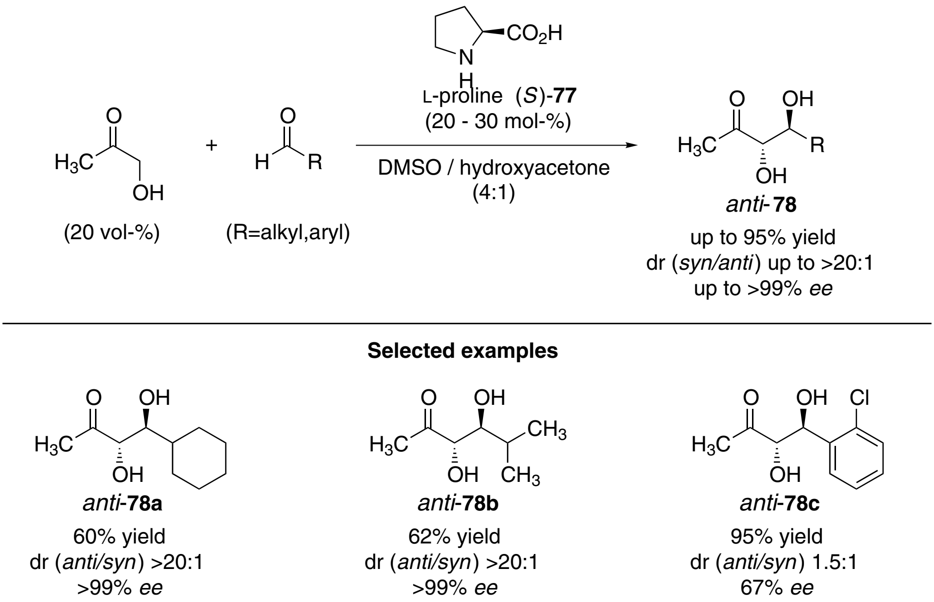
Aldol reactions using L-proline as organocatalysts The concept of the proline-catalyzed aldol reaction has been recently extended by List et al. and the Barbas



Scheme 6.34

group toward the synthesis of aldol products with two stereogenic centers [92–95]. The desired anti-diols have been obtained in a regio-, diastereo-, and enantioselective step starting from achiral compounds.

Substrate range As aldol donor hydroxyacetone was investigated for its potential to form the corresponding optically active anti diols **78** as aldol products [92–94a]. As model reaction the conversion of cyclohexyl carboxaldehyde and hydroxyacetone to the aldol product was investigated in the presence of L-proline as catalyst (because this organocatalyst was found to be very efficient in previous reactions; see also Section 6.2.1.1) [92]. With this catalyst high diastereoselectivity (d.r. > 20:1), and an excellent enantioselectivity (99% ee) were observed. The yield was in the



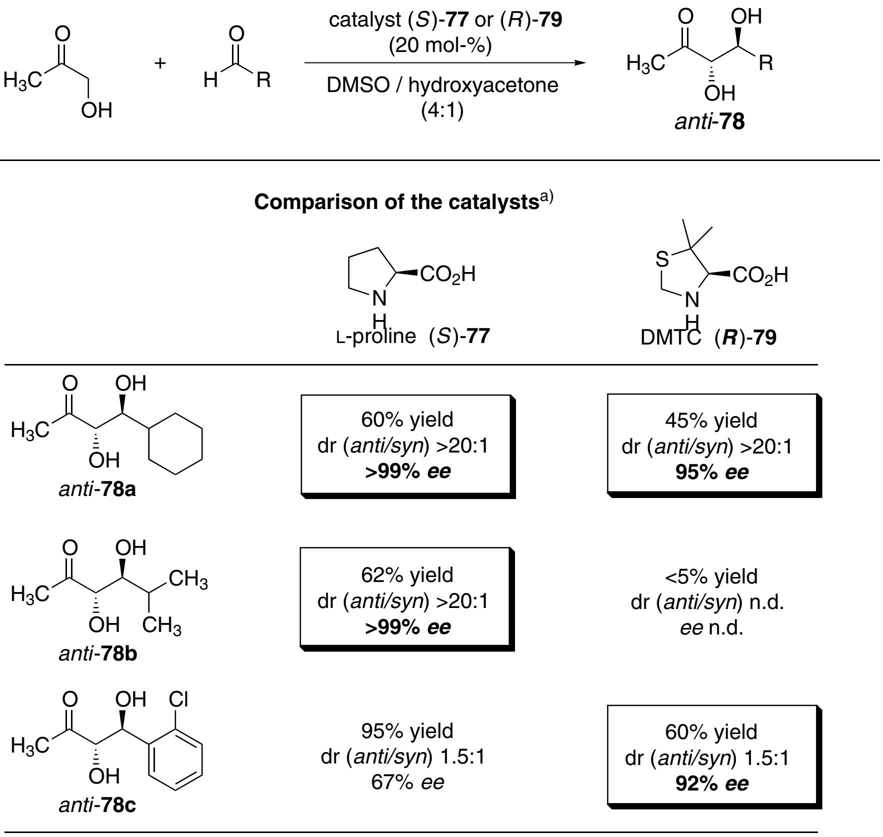
Scheme 6.35

medium range, 60%, and other regioisomers were not found. Impressive diastereo- and enantioselectivity of d.r. > 20:1 and up to >99% ee were also observed when using isobutyraldehyde as substrate (Scheme 6.35).

The reactions also led to high regioselectivity (> 20:1). For alkylated aldehydes unbranched in the α-position, however, low diastereoselectivity (d.r. 1.7:1) and yields of 38% were obtained, although enantioselectivity remained excellent (> 97% ee). Use of aromatic substrates resulted in a d.r. of 1:1 to 1.5:1 only, and the enantioselectivity was in the range 67 to 80% ee [93]. Some representative examples of the L-proline-catalyzed aldol reaction with hydroxyacetone are given in Scheme 6.35.

A possibility of improving ee for aromatic substrates is afforded by the use of DMTC (*R*)-**79** as organocatalyst for this reaction [93]. Because of significantly slower reactions in the presence of DMTC, the syntheses were conducted at elevated temperature of 37 °C. Although yields are usually lower than for reactions using L-proline, with aromatic substrates acceptable yields accompanied by high enantioselectivity (> 90% ee) have been achieved by use of 20 mol% DMTC. Improving the diastereoselectivity remains challenging, however, because DMTC did not give better d.r. ratio [93]. A graphical comparison is given in Scheme 6.36. The catalytic properties of L-proline and DMTC are, therefore, complementary, enabling the aldol reaction of hydroxyacetone with a broad variety of aliphatic and aromatic aldehydes.

Besides hydroxyacetone unmodified cyclic ketones can also serve as suitable donors in the construction of aldol products with two stereogenic centers [94].

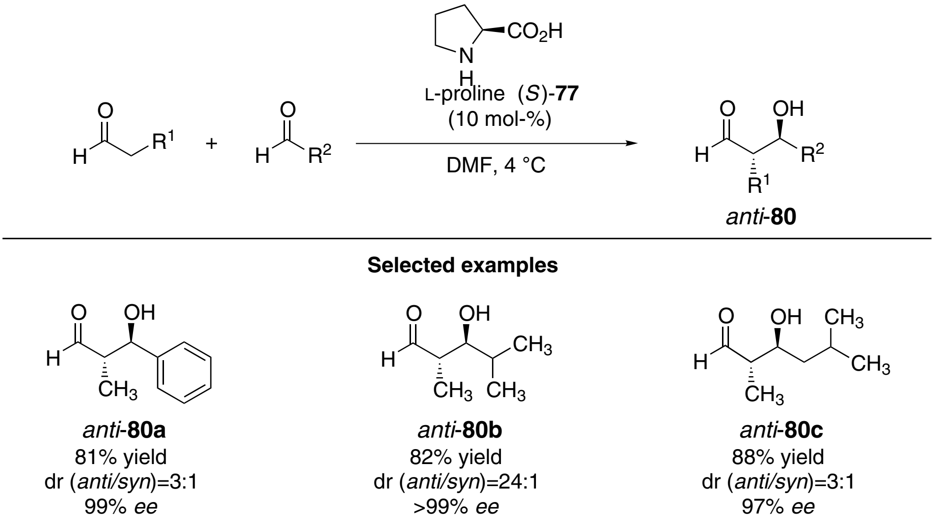


a) Excellent results with respect to enantioselectivity are marked.

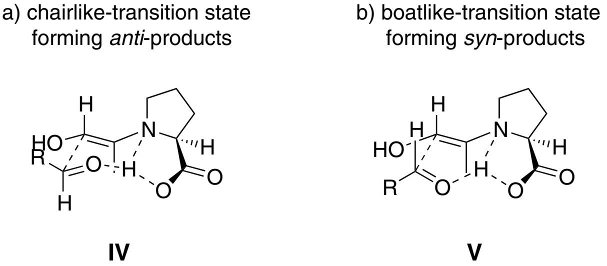
Scheme 6.36

Once again proline functions as organocatalyst furnishing the desired aldol adducts **80** in yields of 41 to 85%. With the exception of alkylated aldehydes branched in the α-position, however, d.r. ratios were low, although good to excellent enantioselectivity of 85 to 97% ee was observed for all aldehydes, irrespective of their substitution pattern. The best result was obtained with isobutyraldehyde; this afforded the anti-aldol product **80b** in 68% yield, with diastereoselectivity of d.r. > 20.1, and enantioselectivity of 97% ee [94, 95].

Mechanism and transition states The basic principles of the proline-catalyzed direct aldol reaction are summarized in Section 6.2.1.1 [93, 94a]. The preferred diastereo- and enantioselectivity were explained in terms of the potential transition states for the aldol reaction using hydroxyacetone shown in Scheme 6.38 [93]. Thus, re-facial attack of the aldehyde at the si face of hydroxyacetone leads to the



Scheme 6.37



Scheme 6.38

formation of a six-membered transitions state **IV** which gives the anti-aldol products. In contrast, reversed facial selectivity of the enamine derived from hydroxyacetone in a boat-like transition state **V** would lead to preferred formation of syn products.

The excellent regioselectivity was explained by highly regioselective enamine formation by the hydroxyacetone, because of the hydroxy group. This π-donating hydroxyl group stabilizes the hydroxyl enamine by interacting with the π^*-orbital of the C=C double bond [93].

A detailed study of the reaction mechanism based on quantum mechanical calculations was reported very recently by Houk and List et al. [96]. In this connection, the ratio of the four stereoisomeric products in the proline-catalyzed diastereo- and enantioselective aldol reaction was predicted and excellent agreement

between the quantum mechanical prediction and the experimental results has been found.

Conclusion

In addition to the asymmetric organocatalytic aldol reaction which forms products with one stereogenic center several powerful methods have been successfully applied to the synthesis of aldol adducts with two stereogenic centers. It is worthy of note that – in contrast with diastereoselective syntheses using chiral auxiliaries – these reactions require achiral starting materials only. The types of catalyst used include optically active phosphoramides, different types of quaternary ammonium salts, and simple amino acids, e.g. proline. Thus, several diastereo- and enantioselective organocatalytic aldol procedures are now available which enable the preparation, in high yields and with excellent regio-, diastereo-, and enantioselectivity, of a broad variety of aldol products bearing a β-hydroxyketone framework with two stereogenic centers. Notably, organocatalytic methodologies for the synthesis of syn – as well as anti-aldol adducts are available.

6.2.2
Intramolecular Asymmetric Aldol Reaction

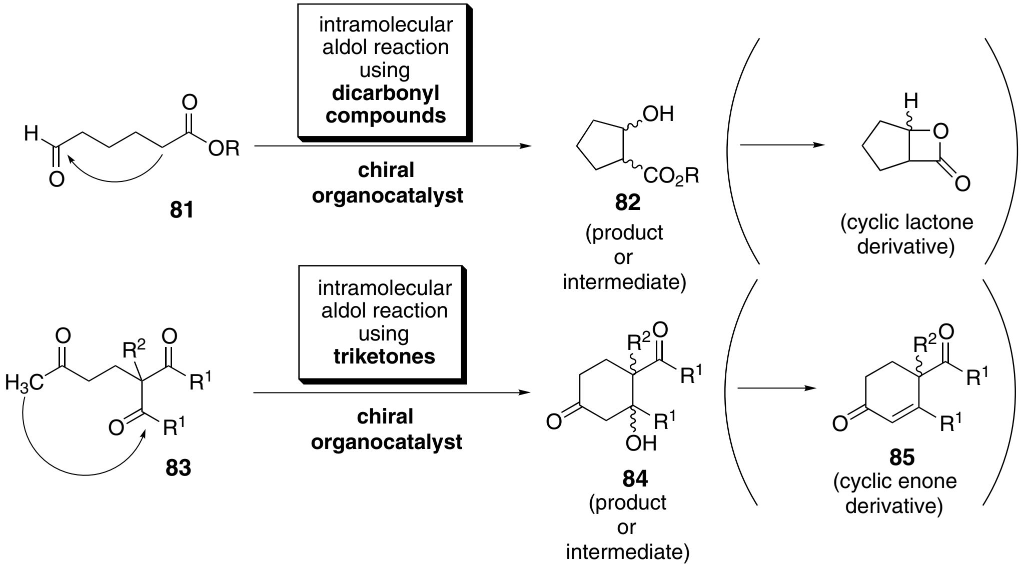
In addition to the many intermolecular asymmetric (organo)catalytic aldol reactions, analogous intramolecular syntheses are also possible. In this connection it is worthy of note that the first example of an asymmetric catalytic aldol reaction was an intramolecular reaction using an organic molecule, L-proline, as chiral catalyst. This reaction – which will be discussed in more detail below – is the so-called Hajos–Parrish–Eder–Sauer–Wiechert reaction [97–101], which was discovered as early as the beginning of the 1970s.

The intramolecular aldol reactions reported so far can be divided into two different types. The first is a enantioselective aldol reaction starting from a dicarbonyl compounds of type **81**. In these reactions, products with two stereogenic centers, **82**, are formed. The reaction is shown in Scheme 6.39, Eq. (1). These products can be converted into derivatives, particularly lactones.

An alternative concept is asymmetric desymmetrization of a prochiral molecule of type **83**. The starting materials **83** have three keto groups and one carbon atom bearing at least three substituents. A prerequisite is the presence of a prochiral carbon atom with two identical substituents bearing a keto functionality (Scheme 6.39, Eq. (2)). This type of asymmetric intramolecular aldol reaction proceeds with formation of cyclic ketols of type **84** with two stereogenic centers. Dehydration can subsequently be performed, leading to optically active enones of type **85**. The two types of intramolecular aldol reaction are shown conceptually in Scheme 6.39.

6.2.2.1 Intramolecular Aldol Reaction Starting from Diketones

It is worthy of note that the type of reaction shown in Scheme 6.39, Eq. (1) was reported only recently [102]. In 2001, Romo and co-workers described an intramolecular, nucleophile-catalyzed aldol-lactonization (NCAL) process which contains



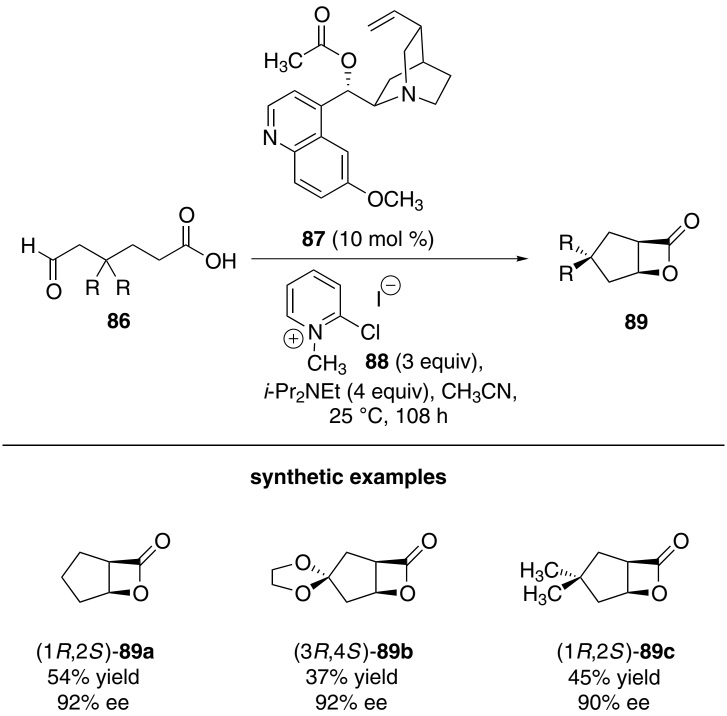
Scheme 6.39

an organocatalytic intramolecular aldol condensation as a key step. 6-Oxohexanoic acids or their disubstituted (prochiral) derivatives were used as starting materials. In the reaction procedure the starting material **86** must be added slowly to a mixture of the catalyst and required additives. In the presence of 10 mol% *O*-acetylquinidine, **87**, as catalyst, three equivalents of the Mukaiyama reagent **88**, and four equivalents of Hünig's base the aldol condensation of the aldehyde acid **86** proceeds, with good enantioselectivity (in the range 90–92% ee) giving the *β*-lactones **89** after subsequent cyclization (Scheme 6.40) [102].

The yields of the products (+)-**89a**–**c** were moderate with 37–54% and the reaction time was somewhat long with 108 h. The opposite enantiomer can be also obtained with high enantioselectivity by use of *O*-acetylquinine as catalyst. In this case the (−) enantiomer of **89a** was formed in 51% yield and with 86% ee.

A detailed study of the effect of modified quinidine derivatives was conducted by the same group [103]. In particular the effects on enantioselectivity of several substituents at the C9 position and of catalyst conformation were investigated, with interesting results – the enantioselectivity was almost unaffected by the *O*-acyl substituent at the C9 carbon atom (Scheme 6.41). For example, use of catalysts **90**, **91**, and **92**, which are based on structurally different acyl substituents, gave the product (1*R*,2*S*)-(+)-**89a** with enantioselectivity in the narrow range 89–92% ee. The yields, however, differed substantially, and did not exceed 54%. Interestingly, a more rigid quinidine derivative resulted in complete reversal of enantioselectivity [103].

A reaction mechanism was proposed in which the tertiary amino group of the alkaloid organocatalyst and the carboxylic acid group form a chiral ammonium



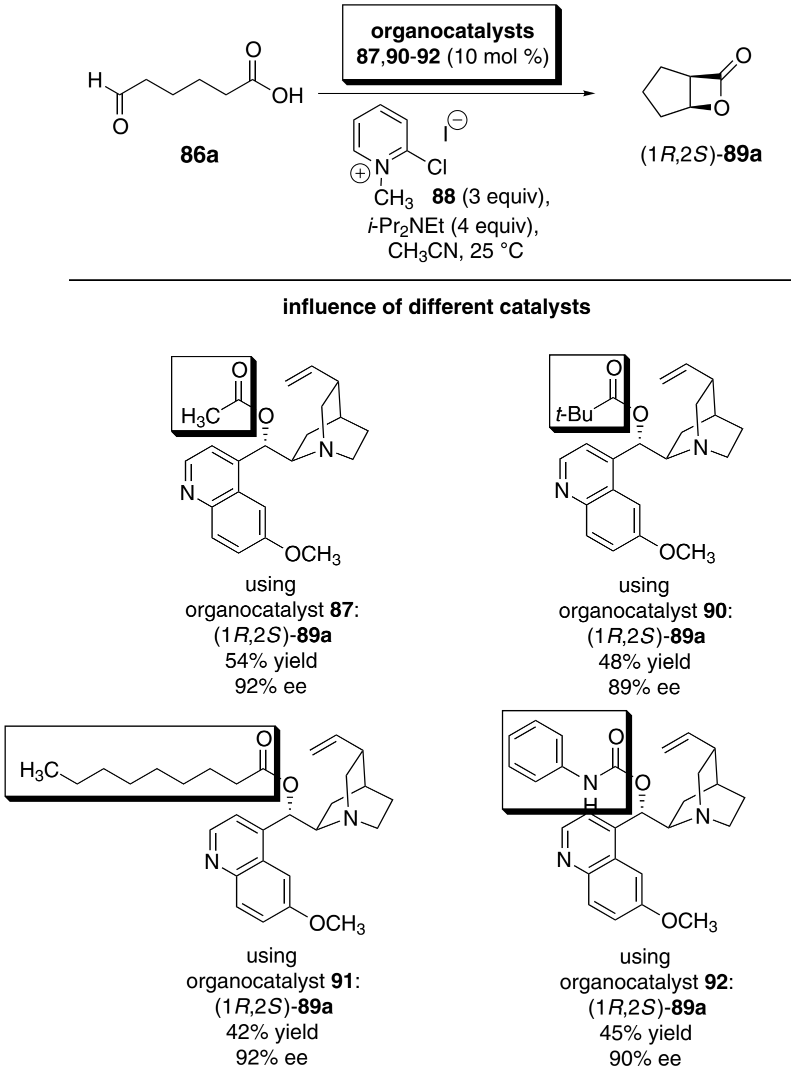
Scheme 6.40

enolate which subsequently reacts enantioselectively with the aldehyde, with formation of the aldolate [102, 103].

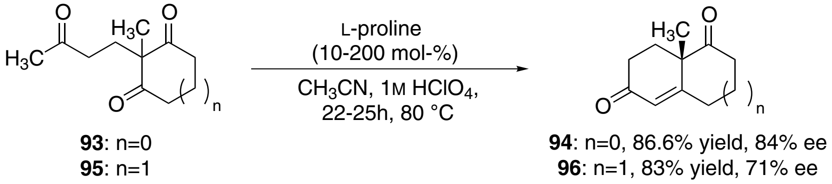
6.2.2.2 Intramolecular Aldol Reaction Starting from Triketones

The intramolecular aldol reaction of triketones with asymmetric desymmetrization has been known for a long time. When Eder, Sauer, and Wiechert [97, 98], and in parallel Hajos and Parrish [99–101] reported this reaction in the early 1970s it was the first example of an asymmetric catalytic aldol reaction, and one of the first examples of an organocatalytic asymmetric synthesis [104].

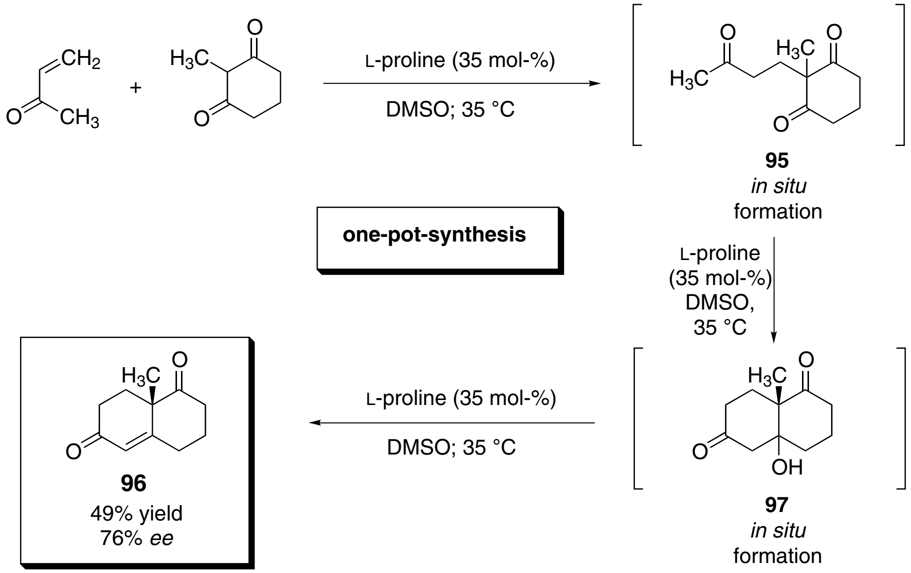
2,2-Disubstituted cyclopentane-1,3-diones and cyclohexane-1,3-diones were used as substrates. After formation of the aldol adducts subsequent intramolecular dehydration furnished products of types **94** and **96**. The asymmetric intramolecular aldol reaction proceeds with a broad variety of natural amino acids as organocatalysts. Among these L-proline was usually found to be the most versatile. For example, conversion of the 2,2-disubstituted cyclopentane-1,3-dione **93** in the presence of L-proline gave the desired product **94** in 86.6% yield and with enantioselectivity of 84% ee [97]. This example and a related reaction with a 2,2-disubstituted cyclohexane-1,3-dione **95** are shown in Scheme 6.42. Chiral induction depends



Scheme 6.41



Scheme 6.42

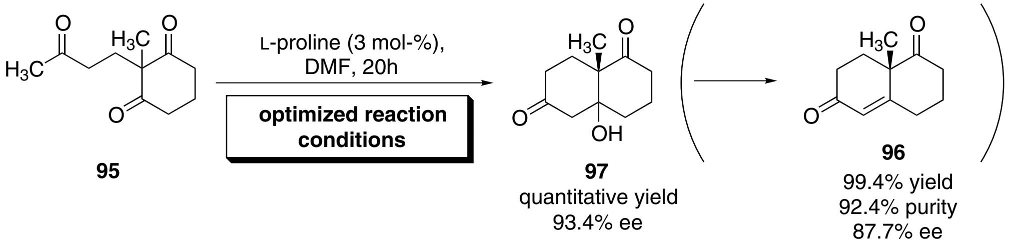


Scheme 6.43

not only on the type of catalyst but also strongly on the solvent and on the nature of the required acid component. This reaction can be also performed with formation of related products with an ethyl substituent at the stereogenic carbon center (instead of a methyl group) [101].

This reaction is particularly suitable for the preparation of the Wieland–Miescher ketone **96**, a very useful building block for construction of a broad variety of biologically active compounds such as steroids, terpenoids, and taxol. On the basis of the proline-catalyzed approach described above Barbas et al. recently reported an optimized procedure for formation of the chiral Wieland–Miescher ketone, **96** [105]. It has been shown that this synthesis (which comprises three reactions) can be performed as a one-pot synthesis. The desired product is obtained in 49% yield with enantioselectivity of 76% ee (Scheme 6.43). Here L-proline functions as an efficient catalyst for all three reaction steps (Michael-addition, cyclization, dehydration). It is also worth noting that although many other amino acids and derivatives thereof were tested as potential alternative catalysts, L-proline had the best catalytic properties for synthesis of **96**. This result emphasizes the superior catalytic properties of proline reported after previous comparative studies by the Hajos group [100, 101].

An investigation by the Hajos group, which included optimization of the reaction conditions, provided detailed insight into the aldol cyclization step and formation of the important intermediate **97** (Scheme 6.44) [101]. The best yield and enantioselectivity were obtained when a polar, aprotic solvent was used. In DMF the aldol cyclization of **95** into the ketol intermediate **97** proceeded in quantitative yield and with high enantiomeric excess of 93.4%. It is worthy of note that a small

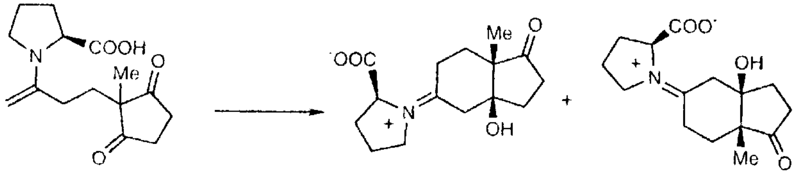


Scheme 6.44

amount – 3 mol% – proline is sufficient for effective catalysis under these conditions. Subsequent dehydration of the ketol **97** gave the enone **96** in 99.4% yield (purity 92.4%) and enantioselectivity 87.7% ee [101]. Solubility of the amino acid organocatalyst was an important prerequisite for catalytic properties. For example, (2*S*,4*R*)-*trans*-4-hydroxyproline, which is insoluble in acetonitrile, did not lead to any reaction whereas the low solubility of proline of 2.6 mg per 100 g is sufficient to catalyze the aldol cyclization efficiently [101].

The first mechanistic explanations of this important synthesis were proposed on the basis of on experimental data by the Parrish [100, 101] and Agami groups [106–110]. Their experiments revealed that the carboxylic acid functionality and the pyrrolidine ring of proline were essential for efficient asymmetric induction. Despite many experimental results from the L-proline-catalyzed intramolecular aldol reaction, however, detailed insight into the mechanism, with regard to enantioselectivity in particular, has not been forthcoming until a recent theoretical study by the Houk group [111, 112]. In this investigation Houk et al. explored transition states and intermediates in the synthesis of the aldol adduct **97**. The ground-state and transition-state structures were located using hybrid density-functional theory. It was found that reaction of **VI** under formation of the cis hydroindanone ketol intermediates, **VIIa** and **VIIb**, is favored over the corresponding trans analogs. In addition, two transitions states, (*S*,*S*)-**VIII** and (*R*,*R*)-**VIII**, leading to the bicyclic aldol intermediates **VIIa** and **VIIb**, respectively, were located (Scheme 6.45). The transition state (*R*,*R*)-**VIII** is less stable than the transition state (*S*,*S*)-**VIII**, which explains the preferred formation of the ketol **IIIa**, and the (*S*) configuration of the final enone product, **96** [112].

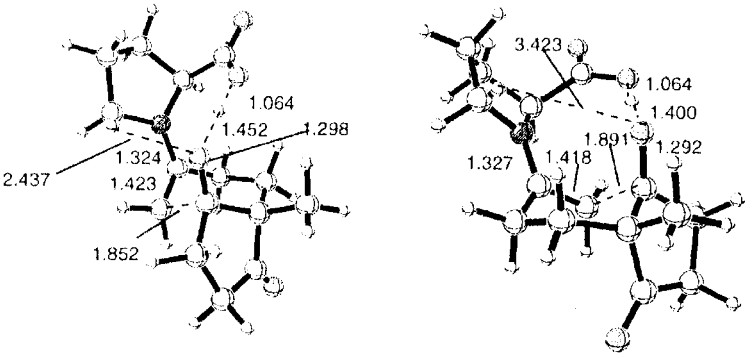
On the basis of the success of these initial reports on the proline-catalyzed intramolecular aldol reaction several groups focused on extending this type of synthesis to bicyclic products bearing angular substituents other than methyl and ethyl reported earlier [97–101]. Preparation of bicyclic systems with protected hydroxymethyl substituents, e.g. **99**, was reported by Uda et al. (Scheme 6.46, Eq. 1) [113, 114]. As a selected example, the aldol adduct **99** was formed in 70% yield and with 75% ee in the presence of one equivalent of L-proline. Synthesis of a related product with an angular phenylthio substituent, **101**, was described by Watt and co-workers (Scheme 6.46, Eq. 2) [115]. After intramolecular proline-catalyzed aldol reaction, dehydration of the ketol intermediate, and subsequent recrystallization



VI **VIIa** **VIIb**

(*S*,*S*)-VIII
E_{act} = 9.1 kcal/mol

(*R*,*R*)-VIII
E_{act} = 12.5 kcal/mol



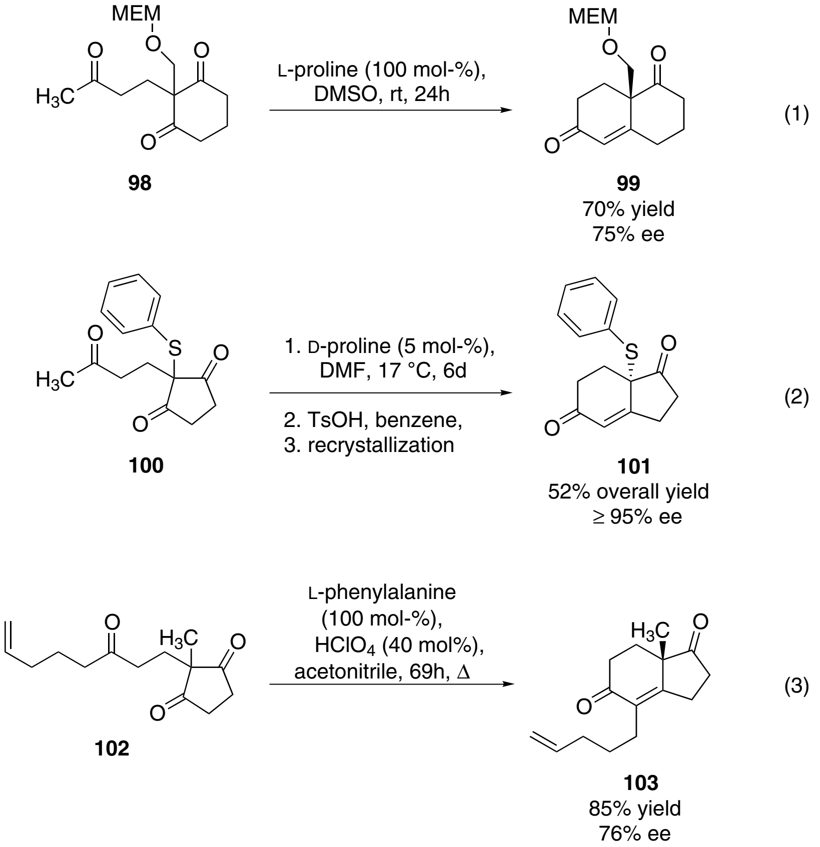
Scheme 6.45 (from Ref. [112] with permission of the ACS)

the product **101** was obtained in 52% overall yield, and with excellent enantioselectivity of ≥95% ee [115].

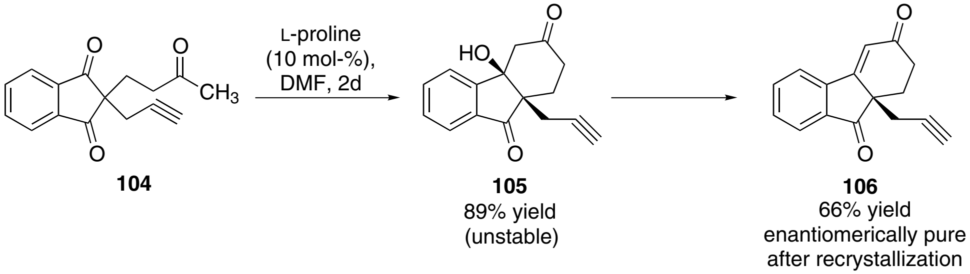
Analogous bicyclic products with different substitution patterns, e.g. **103** [116], were also synthesized (Scheme 6.46, Eq. 3). Compound **103**, which is (in the same way as **96**) also an intermediate in the synthesis of steroids, was prepared starting from **102** in the presence of one equivalent (*S*)-phenylalanine as catalyst [116]. The enantioselectivity of 76% ee was determined after derivatization into a known compound. It is worth noting that for preparation of **103** use of L-proline gave less satisfactory results. A graphical overview of synthesized bicyclic products (related to **96**) with different substituted patterns is given in Scheme 6.46.

The organocatalytic asymmetric intramolecular aldol reaction has also been used in the synthesis of a gibbane framework [117]. The proline-catalyzed aldol cyclization of the triketone **104** into the tricyclic system **106** proceeds *via* the unstable ketol **105** (Scheme 6.47). For this reaction, which occurred at room temperature, a catalytic amount (10 mol%) of L-proline was used. The enone **106** was furnished in 92% yield and a single recrystallization resulted in an enantiomerically pure sample of **106**. This aldol product **106** served as a useful intermediate in the synthesis of the desired gibbane framework.

The Danishefsky group reported the use of an organocatalytic intramolecular aldol reaction in the synthesis of a key intermediate, **108**, for preparation of optically active estrone and commercially relevant 19-norsteroids [118, 119]. In the presence

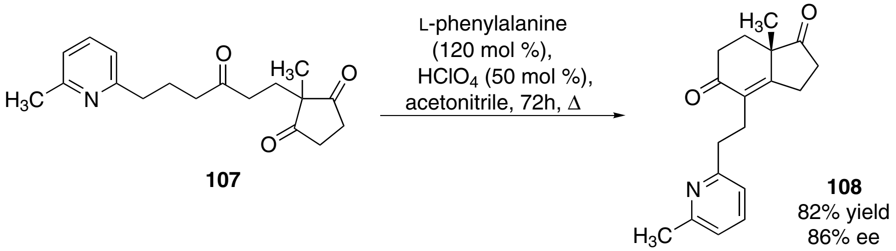


Scheme 6.46



Scheme 6.47

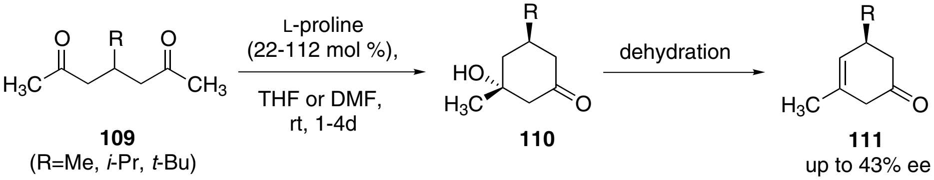
of L-proline as a catalyst and under the "standard" reaction conditions (mentioned above for synthesis of **96**), however, unsatisfactory enantioselectivity of 27% ee was obtained [119]. Significant improvement of the optical purity was achieved on replacing L-proline by L-phenylalanine as organocatalyst. In the presence of stoi-



Scheme 6.48

chiometric amounts of L-phenylalanine cyclization of **107** proceeds efficiently, giving the desired product **108** in 82% yield and with 86% ee (Scheme 6.48) [118]. Subsequently, the product **108** was successfully converted into estrone and 19-norsteroids.

Desymmetrization *via* proline-catalyzed asymmetric intramolecular aldol reaction can, however, also be performed with acyclic diketones of type **109** as has been reported by the Agami group [106]. In the first step a prochiral acyclic diketone reacts in the presence of L-proline as catalyst (22–112 mol%) with formation of the aldol adduct **111** (Scheme 6.49). In this step reaction products with two stereogenic centers, **110**, are formed. These chiral hydroxyketones **110** are subsequently converted, *via* dehydration, into the enones **111**, by treatment with *p*-toluenesulfonic acid.

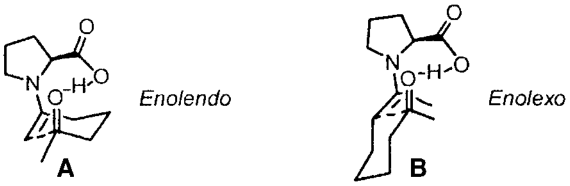


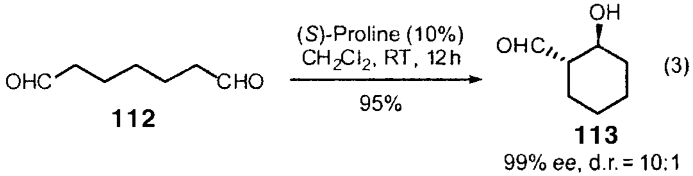
Scheme 6.49

Although the highest enantiomeric excess of the products was 43% only, in principle this route is an interesting and promising means of producing cyclic enones with a chiral center by use of a readily available catalyst.

6.2.2.3 **Intramolecular Aldol Reaction Starting from Dialdehydes**

A highly diastereo- and enantioselective synthesis of trans-1,2-disubstituted cyclohexanes by means of the first direct catalytic asymmetric 6-enolexo aldolization has been developed very recently by the List group [120] (previously only 6-enolendo aldolizations had been reported). Dialdehydes were usually used as starting materials and proline was a very efficient catalyst for this reaction also. A selected example of this 6-enolexo-aldolization is given in Scheme 6.50; in this





Scheme 6.50 (from Ref. [120])

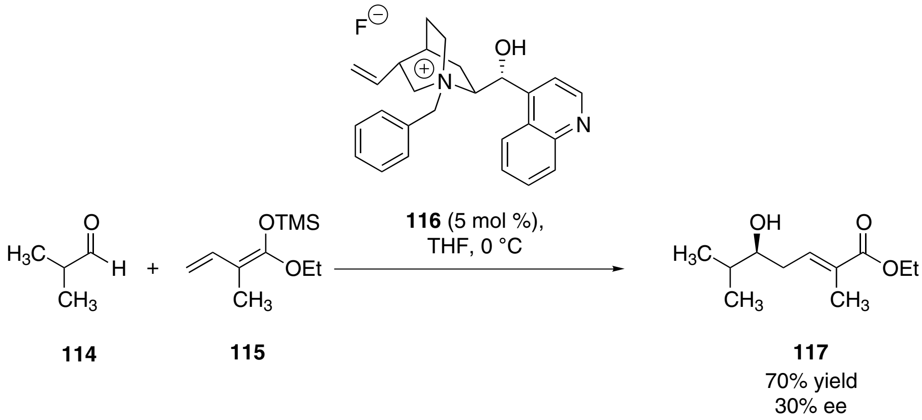
example the desired trans-1,2-disubstituted cyclohexane product is obtained with a diastereomeric ratio of d.r. = 10:1 and impressive enantioselectivity of 99% ee [120]. Excellent enantioselectivity is also obtained when substituted heptanedials are used as starting materials. This method is, therefore, an efficient means of preparation of optically active β-hydroxy cyclohexane carbonyl derivatives **113**. This 6-enolexo aldolization is expected to proceed via chair-like-transition state (transition state **B** in Scheme 6.50).

In conclusion, there have been many reports of the high synthetic potential of the intramolecular aldol reaction in the enantioselective construction of cyclic enones. In particular the proline-catalyzed desymmetrization of triketones has been widely used for formation of optically active bicyclic systems which are versatile building blocks for steroids and other biologically active compounds.

6.2.3
Modified Aldol Reactions – Vinylogous Aldol, Nitroaldol, and Nitrone Aldol Reactions

In addition to the "classic" aldol reaction described, e.g., in Sections 6.2.1 and 6.2.2, several "modified" versions have been reported. These methods are based on the use of nucleophiles related to the standard ketones. In particular, γ-dienolates, nitromethane, and nitrones are interesting carbon nucleophiles in aldol reactions and the use of these types of substrate has been investigated in aldol reactions catalyzed by organocatalysts.

To start with the addition of γ-dienolates to aldehydes, the so-called vinylogous Mukaiyama aldol reaction, Campagne et al. studied the applicability of different types of catalyst when using the silyldienolate **115** as nucleophile [121]. In general, many products obtained by means of this type of reaction are of interest in the total synthesis of natural products. It should be added that use of CuF-(*S*)-TolBinap (10 mol%) as metal-based catalyst led to 68% yield and enantioselectivity up to



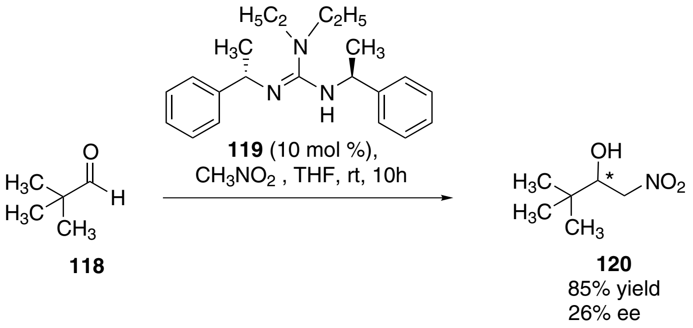
Scheme 6.51

77% ee [121]. With regard to the type of organocatalyst investigated, Campagne et al. focused on alkaloid-based phase-transfer catalysts; fluoride was always used as counter-ion. Although different types of alkaloid-based catalyst were used, enantioselectivity remained low – 30% ee or below [121]. It is worthy of note, however, that the regioselectivity was excellent. Products of type **117** were obtained in yields up to 70%. A representative example is shown in Scheme 6.51.

The asymmetric catalytic nitroaldol reaction, also known as the asymmetric Henry reaction, is another example of an aldol-related synthesis of high general interest. In this reaction nitromethane (or a related nitroalkane) reacts in the presence of a chiral catalyst with an aldehyde, forming optically active β-nitro alcohols [122]. The β-nitro alcohols are valuable intermediates in the synthesis of a broad variety of chiral building blocks, e.g. β-amino alcohols. A highly efficient asymmetric catalytic nitroaldol reaction has been developed by the Shibasaki group, who used multifunctional lanthanoid-based complexes as chiral catalysts [122–125].

In addition to this highly enantioselective metal-catalyzed approach, several organocatalytic versions of the asymmetric nitroaldol reaction have recently been reported. The Najera group used enantiomerically pure guanidines with and without C_2 symmetry as chiral catalysts for the addition of nitromethane to aldehydes [126]. When the reaction was conducted at room temperature β-nitro alcohols of type **120** were obtained in yields of up to 85% but enantioselectivity, 26% ee or below, was low. A selected example is given in Scheme 6.52. Higher enantioselectivity, 54% ee, can be obtained at a low reaction temperature of −65 °C, but the yield (33%) is much lower.

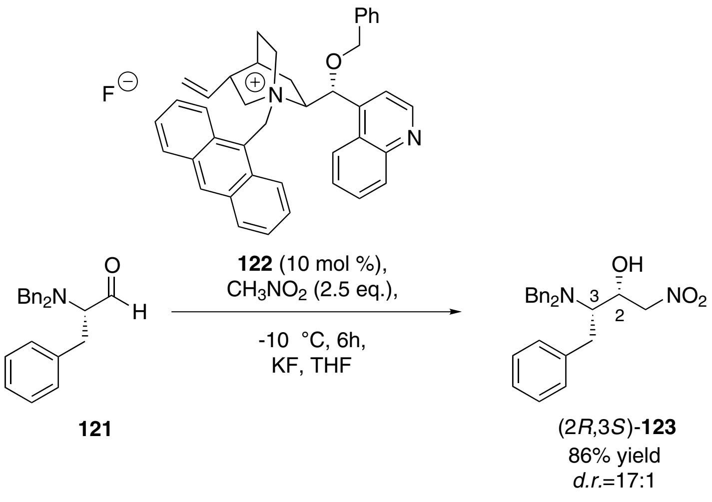
The enantioselective nitroaldol reaction in the presence of alkaloid-based organocatalysts has been investigated by the Matsumoto group [127]. A further focus of this study was investigation of the effect of high pressure on the course of the reaction. Addition of nitromethane to benzaldehyde at atmospheric pressure resulted in a low (4%) yield and 18% ee when a catalytic amount (3 mol%) quinidine was



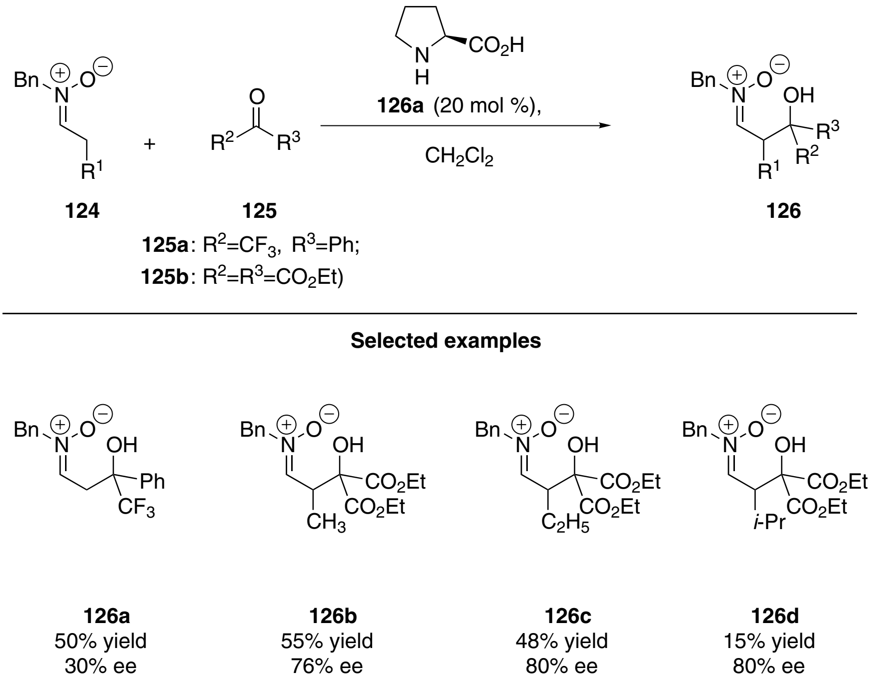
Scheme 6.52

used. Higher yields were obtained by increasing the pressure, although enantioselectivity decreased substantially. For example, at 7000 bar the yield improved to 80% but enantioselectivity was low – only 3% ee. Analogous reactions were also performed with ketones. The best result (81% yield, 21% ee) was obtained by use of trifluoroacetophenone as substrate, atmospheric pressure, a low reaction temperature (−78 °C), and a catalytic amount (20 mol%) of quinidine.

Use of an organocatalyst in a highly diastereoselective nitroaldol reaction was reported by the Corey group in the synthesis of **123** [128]. This compound is a key building block in the synthesis of the HIV-protease inhibitor amprenavir. The alkaloid-based fluoride salt, **122**, was used as an efficient chiral phase-transfer catalyst (this type of catalyst was developed by the same group [129–131]) and led to formation of the (2*R*,3*S*) diastereomer (2*R*,3*S*)-**123** in 86% yield and with a diastereomeric ratio of d.r. = 17:1 (Scheme 6.53) [128]. It is worthy of note that a much



Scheme 6.53

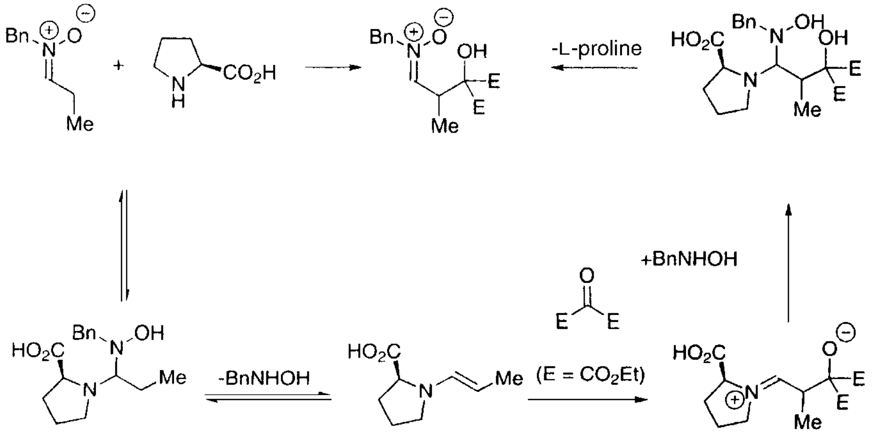


Scheme 6.54

lower diastereomeric ratio of d.r. 4:1 was obtained when an achiral phase-transfer catalyst was used. The Corey group also found a related organocatalyst (containing a different nitrogen substituent) which led to highly diastereoselective formation of the (2*S*,3*S*) diastereomer [128]. The diastereoselectivity of this nitroaldol reaction can therefore be controlled by the *N*-substituent of the alkaloid catalyst.

The first catalytic asymmetric aldol-type reaction of nitrones was recently reported by the Jørgensen group [132]. Screening of catalysts revealed that L-proline is preferred and leads to β-hydroxynitrones with moderate to high enantioselectivity. In the presence of 20 mol% L-proline, trifluoroacetophenone **125a** was converted into the adduct **126a** in 50% yield and with 30% ee (Scheme 6.54). When diethyl ketomalonate **125b** was used as substrate significantly higher enantioselectivity in the range 76–80% ee was obtained for products **126b–d** (Scheme 6.54). Aldehydes are not suitable substrates because the β-hydroxynitrones formed undergo elimination reactions leading to the corresponding α,β-unsaturated compounds. In addition to L-proline the dipeptide L-Pro-L-Leu was also found to be a suitable catalyst, giving comparable yield and enantioselectivity for product **126a** (46% yield, 29% ee) [132].

With regard to the mechanism of this new type of reaction, the Jørgensen group postulated enamine formation, by addition of the catalyst to the nitrone, followed by hydroxylamine elimination [132]. Subsequent aldol-type reaction of this enamine with the carbonyl component and release of the proline catalyst by exchange



Scheme 6.55 (from Ref. [132])

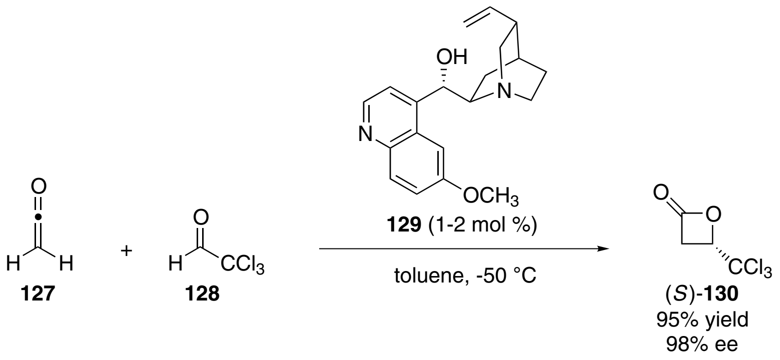
with a hydroxylamine are the next steps in this catalytic cycle. This reaction mechanism, shown in Scheme 6.55, is supported by kinetic data and by analysis of intermediates and products [132].

It should be added that improved formation of products of type **126** was achieved by choosing a different reaction strategy [133]. A "typical" proline-catalyzed aldol reaction (starting from aldehydes as donors and compounds **125** as acceptors), followed by conversion of the C=O functionality of the aldol adduct into a nitrone group by condensation with a hydroxylamine component led to products of type **126** in good yield and with high enantioselectivity (up to 96% ee) [133].

In summary, several reports have shown that asymmetric "modified" aldol reactions using γ-dienolates, nitroalkanes, or nitrones as donors can (in principal) be performed by use of organocatalysts. Often, however, enantioselectivity is moderate only, and must still be improved. Because these organocatalytic reactions give important intermediates, e.g. for synthesis of pharmaceuticals, it can be expected that this field of "modified" aldol reactions with organocatalysts will gain further synthetic importance in the future.

6.3
β-Lactone Synthesis *via* Ketene Addition

Asymmetric addition of ketenes to aldehydes is a highly attractive synthetic access to β-lactones with perfect "atom economy" [134, 135]. This reaction can be catalyzed efficiently by using chiral amines as organocatalysts. As early as 1967 Borrmann et al. described an organocatalytic asymmetric ketene addition to aldehydes [136]; chiral tertiary amines, in particular (−)-*N*,*N*-dimethyl-α-phenylethylamine or (−)-brucine, were used as catalysts [136]. The resulting lactones were obtained with modest enantioselectivity of up to 44% ee.



Scheme 6.56

An impressive highly enantioselective route to *β*-lactones in which cinchona alkaloids were used as organocatalysts was reported by Wynberg et al. in 1982 [137]. The Wynberg group found that in the presence of only 1–2 mol% quinidine, **129**, as catalyst addition of ketene, **127**, to chloral, **128**, at −50 °C proceeds highly enantioselectively. After work-up the desired product (*S*)-**130** was isolated in a high yield, 95%, and with excellent enantioselectivity of 98% ee (Scheme 6.56) [137]. Intensive catalyst screening revealed that quinidine was the most efficient catalyst for formation of the (*S*) enantiomer. The (*R*) enantiomer can be obtained by use of quinine, which gave the product (*R*)-**130** with 76% ee. The gaseous ketene was prepared *via* pyrolysis of acetone and subsequently bubbled through the reaction solution. An important application of products of type **130** has been also demonstrated by the Wynberg group, who easily converted product **130** into enantiomerically pure malic acid [134, 137]. This process found technical application by Lonza in the large scale synthesis of optically active malic and citramalic acids [138]. With regard to the reaction mechanism, because the ketene first acylates the free hydroxyl group of the alkaloid, the "real" catalytically active species is the alkaloid ester [134].

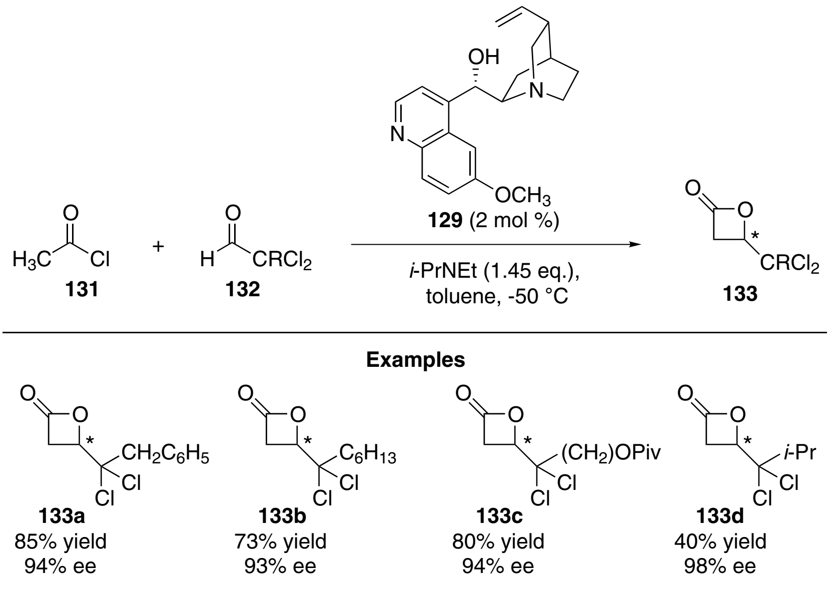
Another study by the Wynberg group focused on the range of carbonyl component substrates [139, 140]. At first several chlorinated aldehydes (related to chloral) were used in the reaction with ketene. The reactions proceeded in the presence of a catalytic amount (1–2 mol%) of the chiral alkaloid catalyst, either quinidine or quinine. The resulting products were formed in good yields, 67–95% [139]. Higher enantioselectivity was usually obtained by use of quinidine (up to 98% ee) rather than quinine (up to 76% ee). Interestingly, the reaction also proceeds well when ketones bearing a trichloromethyl substituent are used as substrates; in the presence of quinidine as catalyst yields were up to 95% and enantioselectivity was between 89 and 94% ee. Once again, use of quinine resulted in somewhat lower enantioselectivity [139].

Polymer-supported organocatalysts have been used for cycloaddition of ketene, **127**, to chloral, **128** [141]. Use of homo-acrylate polymers of cinchona alkaloids led to formation of the desired *β*-lactone (*S*)-**130** with enantioselectivity up to

94% ee. Enantioselectivity was therefore comparable with that obtained with the non-immobilized cinchona alkaloid catalysts.

Although this Wynberg process for *β*-lactones is highly efficient, the need for activated aldehydes and the required ketene generator limits the general nature of this synthetic route. Addressing the latter issue, Romo et al. developed a modified process based on *in situ*-generation of the ketene [142a]. Although, in principle, *in situ* generation of ketenes is readily achievable by dehydrochlorination of acid chlorides, catalyzed by tertiary amines, there were two major challenges to use of this procedure in the Wynberg *β*-lactone synthesis – racemic *β*-lactone formation catalyzed by the achiral tertiary amine had to be avoided and the possibility of the chiral quinidine catalyst acting as a base in the dehydrohalogenation process and rendering it unavailable for the asymmetric catalytic process had to be suppressed. These potential side reactions can be avoided by use of a suitable combination of tertiary amine and chiral organocatalyst consisting of stoichiometric amounts of Hünig's base in the presence of 2 mol% quinidine. By using this combination, and dichlorinated aldehydes as substrates, the Romo group obtained the desired products of type **133** with high enantioselectivity of 93–98% ee (Scheme 6.57) [142a]. The yields, however, varied in a wide range – between 40 and 85%. Toluene was, in general, found to be very useful as solvent. When trichloroacetone was used as the ketone component a low yield (25%) was obtained.

Very recently, the Nelson group expanded scope of this reaction by applying cinchona alkaloid–Lewis acid catalyst systems [142b]. In the presence of *O*-trimethylsilylated quinine or quinidine, and $LiClO_4$ as Lewis acid cocatalyst, a broad range of aliphatic and aromatic aldehydes was converted into the corresponding

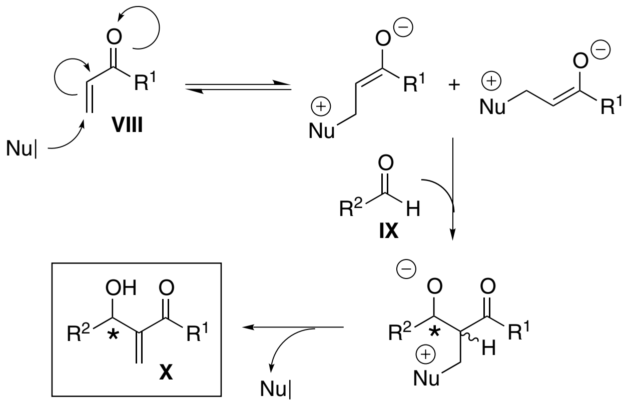


Scheme 6.57

β-lactones very efficiently, e.g. with up to >99% ee [142b]. In summary, alkaloid-catalyzed addition of ketenes to activated aldehydes enables highly attractive access to β-lactones with excellent enantioselectivity. A major challenge in the future will certainly be extension of this method toward the use of non-activated aldehydes as starting materials.

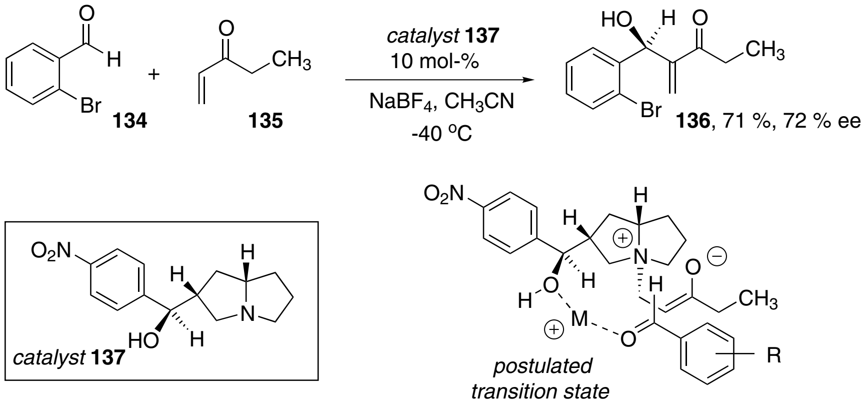
6.4
The Morita–Baylis–Hillman Reaction

The Morita–Baylis–Hillman (MBH) reaction is the formation of α-methylene-β-hydroxycarbonyl compounds **X** by addition of aldehydes **IX** to α,β-unsaturated carbonyl compounds **VIII**, for example vinyl ketones, acrylonitriles or acrylic esters (Scheme 6.58) [143–148]. For the reaction to occur the presence of catalytically active nucleophiles ("Nu", Scheme 6.58) is required. It is now commonly accepted that the MBH reaction is initiated by addition of the catalytically active nucleophile to the enone/enoate **VIII**. The resulting enolate adds to the aldehyde **IX**, establishing the new stereogenic center at the aldehydic carbonyl carbon atom. Formation of the product **X** is completed by proton transfer from the α-position of the carbonyl moiety to the alcoholate oxygen atom with concomitant elimination of the nucleophile. Thus "Nu" is available for the next catalytic cycle.



Scheme 6.58

The reaction sequence depicted in Scheme 6.58 also illustrates several problems associated with the MBH reaction. Addition to aldehyde **IX** can be slow, and side-reactions such as base-induced polymerization of the α,β-unsaturated carbonyl compound can occur. Furthermore, generation of diastereomeric (i.e. *E*/*Z*) enolates can complicate matters if enantioselective addition to the aldehyde component is desired. In principle, formation of a stereogenic center at the aldehydic carbonyl C-atom can be steered by: (i) use of a chiral α,β-unsaturated carbonyl compound [149, 150]; (ii) use of a chiral aldehyde; and (iii) use of a chiral nucleophilic cata-

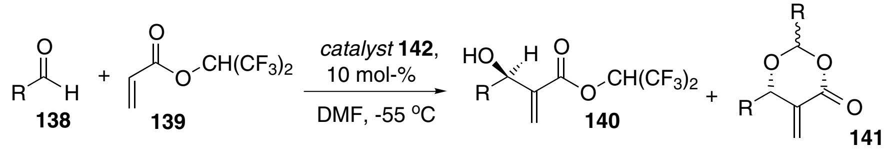


Scheme 6.59

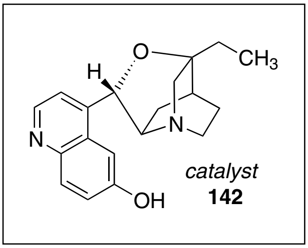
lyst. In the context of this section, the catalytic enantioselective version, i.e. (iii), of the MBH reaction will be considered exclusively.

Early attempts by Drewes et al. [147], Izaacs et al. [149], and Markó et al. [151] to effect a catalytic asymmetric MBH reaction concentrated on the use of chiral and readily available nitrogen bases such as brucine, *N*-methylprolinol, *N*-methylephedrine, nicotine, quinine, quinidine, etc. [147, 149, 151]. With these catalysts only moderate enantioselectivity ($< 20\%$) could be achieved. Under high-pressure conditions (5 kbar), Hirama et al. achieved addition of *p*-nitrobenzaldehyde to methyl vinyl ketone with 47% ee, by use of a C_2-symmetric DABCO derivative as the chiral catalyst [152]. Enantioselectivity $> 70\%$ was achieved for the first time by Barrett et al., by use of the proline-based chiral pyrrolizidine catalyst **137**. In the presence of ca. 10 mol% of this chiral base (**137**), *o*-bromobenzaldehyde (**134**) could be coupled with ethyl vinyl ketone (**135**), affording the Baylis–Hillman product **136** in 71% yield and 72% enantiomeric excess (Scheme 6.59) [153]. Other substituted benzaldehydes afforded comparable yields and enantioselectivity. The reaction shown in Scheme 6.59 was conducted at -40 °C and at ambient pressure, and it is interesting to note that both efficiency and enantioselectivity relied on the use of sodium tetrafluoroborate as co-catalyst. It was argued that the alkali metal ion effects coordination of the acceptor carbonyl oxygen (aldehyde **134**) to the hydroxyl group of the catalyst and thus effects proper orientation for face-selective coupling of the catalyst-bound enolate anion and the aldehyde (Scheme 6.59) [153].

Enantioselectivity as high as 99% was achieved by Hatakeyama et al. in the coupling of a variety of aldehydes **138** with the very electrophilic 1,1,1,3,3,3-hexafluoro-2-propyl acrylate **139** (Scheme 6.60) [154a]. As summarized in Scheme 6.60 (top), the MBH product **140** was obtained in 31–58% yield and with enantiomeric excess up to 99%. Reaction times were approximately 1 h (R = *p*-NO_2-Ph) up to 72 h (R = *c*-hexyl). It was revealed by systematic screening of reagent–catalyst combinations that this example of a highly enantioselective MBH reaction requires both the strongly electrophilic acrylate **139** and the cinchonine derivative **142** [154a]. Preparatively, the concomitant formation of the dioxanone derivatives **141** is somewhat

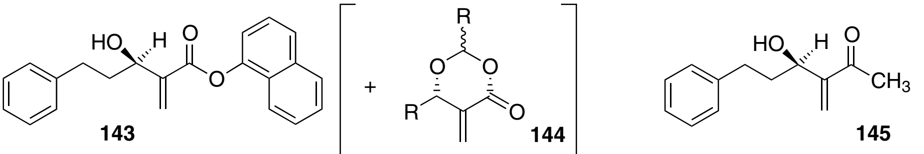


Hatakeyama et al.
(Ref. 154a)



R	Yield [%], configuration, ee [%]	
	Ester **140**	Dioxanone **141**
p-NO2Ph	58, *R*, 91	11, *R*, 4
Ph	57, *R*, 95	- - -
E-Ph-CH=CH	50, *R*, 92	- - -
Et	40, *R*, 97	22, *S*, 27
i-Bu	51, *R*, 99	18 *S*, 85
i-Pr	36, *R*, 99	25, *S*, 70
c-hexyl	31, *R*, 99	23, *S*, 76

Shi and *Jiang*
(Ref. 154b)



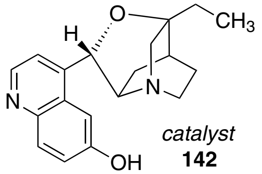
10 mol-% catalyst **142**
THF, r.t.: 50 %, 70 % ee
THF, -20 °C: 17 %, 92 % ee

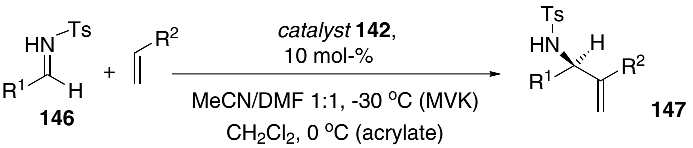
R = Ph-CH2CH2-
r.t.: 23 %, 10 % ee
-20 °C: 59 %, 20 % ee

10 mol-% catalyst **142**
THF, -30 °C: 69 %, 49 % ee

Scheme 6.60

disadvantageous – these side-products are formed with opposite sense asymmetric induction and must be separated. Shi and Jiang examined the performance of the catalyst **142** in the MBH reaction of aldehydes with MVK (methyl vinyl ketone) and methyl α-naphthylacrylate [154b]. As summarized in Scheme 6.60 (bottom), enantiomeric excesses were 92% with the α-naphthylacrylate (MBH product **143**, with the dioxanone **144** as by-product) and 49% with MVK (**145**). Shi et al. furthermore observed a synergistic effect of L-proline with Lewis bases such as imidazole, DABCO etc. in the catalysis of the MBH reaction [154c]. The same dual catalyst approach was followed by Miller et al. for the asymmetric addition of MVK to aldehydes: By the combined action of L-proline and an octapeptide, enantiomeric ex-





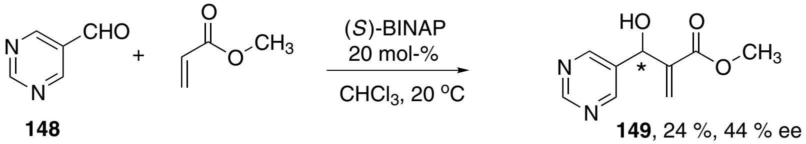
		Addition product **147**		
R^1	R^2	Yield [%]	ee [%]	Config.
Ph	$COCH_3$	80	97	*R*
Ph	CO_2CH_3	62	83	*R*
p-Me-Ph	$COCH_3$	76	96	*R*
p-Me-Ph	CO_2CH_3	67	80	*R*
p-MeO-Ph	$COCH_3$	64	99	*R*
p-MeO-Ph	CO_2CH_3	64	70	*R*
m-F-Ph	$COCH_3$	55	90	*R*
m-F-Ph	CO_2CH_3	87	83	*R*
p-Cl-Ph	CO_2CH_3	60	77	*R*
p-NO_2-Ph	$COCH_3$	60	74	*R*
2-furyl	$COCH_3$	58	73	*R*

Scheme 6.61

cesses in the range 63–81% were achieved in the addition of MVK to a series of aryl aldehydes [154d].

Shi and Xu reported that the chiral amine catalyst **142** also performs quite efficiently in the related addition of *N*-tosyl aryl imines to methyl vinyl ketone (MVK), to methyl acrylate, and to acrylonitrile (Scheme 6.61) [155]. As shown in Scheme 6.61, enantiomeric excesses > 95% were achieved for several *β*-*N*-tosylamino enones **147** obtained by addition of aryl imines (**146**) to MVK, ≥80% for addition to methyl acrylate, and 55% ee (max.) for addition to acrylonitrile (not shown in Scheme 6.61). Reaction times were typically 1–3 days. *N*-Sulfonylimines derived from aliphatic aldehydes gave rise to complex product mixtures. Under the reaction conditions shown in Scheme 6.61 addition of *p*-nitrobenzaldehyde to MVK proceeded with only 20% ee.

In addition to nitrogen bases, the potential of chiral phosphanes as catalysts has also been assessed. Early work on the use of *P*-chiral phosphines in intramolecular



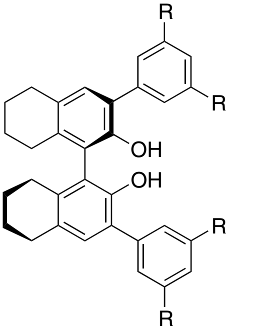
Scheme 6.62

versions of the MBH reaction afforded only low ee (up to 14%) [156]. Better enantioselectivity was achieved by Soai et al. by using (*S*)-BINAP in the addition of pyrimidine-5-carbaldehyde **148** to methyl acrylate (Scheme 6.62) [157]. In this process, which required 20 mol% chiral phosphane catalyst, MBH adduct **149** with up to 44% ee was obtained. Quite remarkable progress was achieved by Schaus and McDougal by using *achiral* triethylphosphane in the presence of BINOL derivatives as *chiral* Brønsted acids (Scheme 6.63) [158]. As summarized in Scheme 6.63, use of 10 mol% 3,3′-disubstituted octahydro-BINOL derivatives **150a** and **150b** resulted in excellent ee (up to 96%) for the MBH addition products **151**. The yields and ee summarized in Scheme 6.63 were obtained after 48 h reaction. It is believed that the chiral Brønsted acids promote conjugate addition of the phosphane, by protonation the carbonyl oxygen atom, and then remain hydrogen bonded to the resulting enolate in the enantioselectivity-determining aldehyde-addition step (see Scheme 6.58) [158].

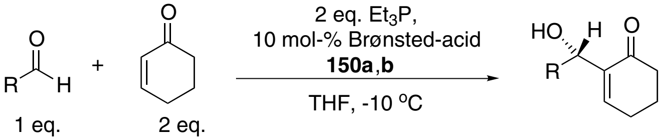
In the presence of Lewis acids such as $BF_3{\cdot}Et_2O$ thioethers promote the MBH addition to enones also [159]. Goodman et al. synthesized the C_2-symmetric chiral thioether **152** and used it in the MBH addition of a variety of aldehydes to MVK (Scheme 6.64) [160]. As summarized in Scheme 6.64, enantiomeric excesses up to 49% were achieved in this MBH reaction. Interestingly, only very short reaction times (30–120 min) were needed, albeit at overstoichiometric catalyst loading.

An alternative approach to the enantioselective MBH coupling of aldehydes with vinylic ketones was presented by Barrett et al. (Scheme 6.65) [161]. In the first step, coupling of the two components is effected by a third reagent, trimethylsilylphenyl sulfide or selenide. Formation of the *β*-phenylthio or *β*-phenylseleno carbonyl intermediates **154a**,**b** is effected by the acyloxy borane **155**. In the presence of 20 mol% of the borane catalyst the addition products **154a**,**b** were obtained with excellent syn/anti (**154a**/**154b**) ratios ($\geq$ 95:5) and with enantiomeric excess typically >95%. For propionic aldehyde and methyl vinyl ketone as substrates > 97% ee was achieved. Similar selectivity is obtained with both the sulfur- and the selenium-based reagents TMS-X-Ph. In the second step, elimination of the phenylthio or phenylseleno substituents is effected by treatment with oxidants such as hydrogen peroxide or *m*-chloroperbenzoic acid. Clearly, elimination of the selenoxide proceeds more readily than that of the sulfoxide. For the latter heating to 130–150 °C completes the sequence whereas for selenium smooth elimination occurs at 25 °C. The overall procedure affords the MBH products **156** with up to 96% enantiomeric excess.

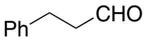
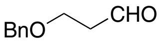
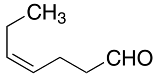
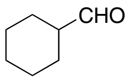
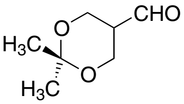
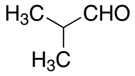
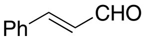
chiral Brønsted-acids **150a**,**b**:



150a: R = $-CH_3$
150b: R = $-CF_3$

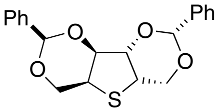


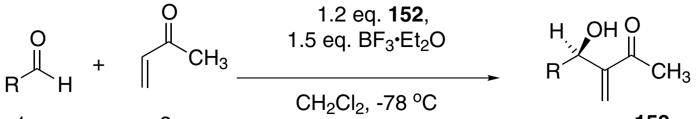
151

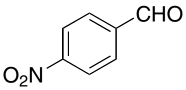
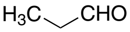
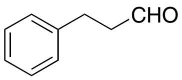
Aldehyde	Brønsted-acid	Addition product **151**	
		Yield [%]	ee [%]
	**150b**	88	90
	**150b**	74	82
	**150a**	72	96
	**150a**	71	96
	**150a**	70	92
	**150a**	82	95
Ph–CHO	**150b**	40	67
	**150a**	39	81

Scheme 6.63

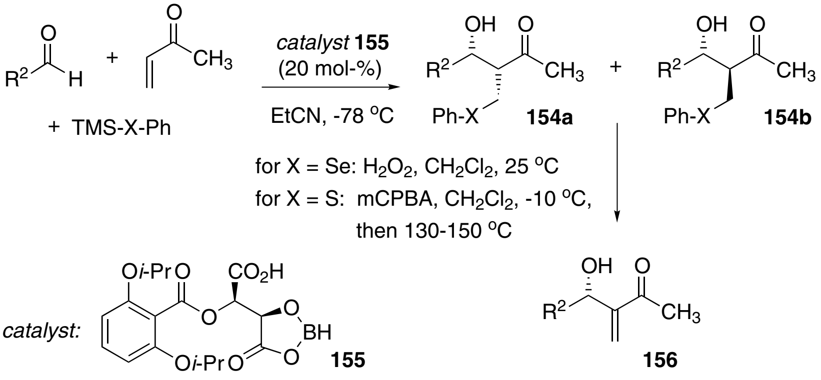
catalyst **152**:





Aldehyde	Addition product **153** Yield [%]	ee [%]
	38-48	46-49
	60	23
	41	14

Scheme 6.64



Scheme 6.65

Conclusions

The MBH reaction is, synthetically, a very appealing transformation. The chiral α-methylene-β-hydroxycarbonyl products are valuable intermediates in organic synthesis. Three catalytic asymmetric versions of the MBH addition affording > 90% enantiomeric excess have so far been reported. Two (Hatakeyama et al. [154a] and Shi and Jiang [154b]) use a modified *cinchona* alkaloid as the chiral nucleophilic catalyst. The third, and most recent, example by Schaus and McDougal [158] is based on the novel approach of combining an achiral phosphane catalyst with a chiral Brønsted acid (BINOL derivatives). The latter approach – which affords good chemical yields and excellent ee using fairly readily available catalysts – has potential for adaptation to numerous substrate classes. The alternative two-step approach reported by Barrett et al. [161] enables complementary and alternative access to enantiomerically highly enriched α-methylene-β-hydroxycarbonyl compounds.

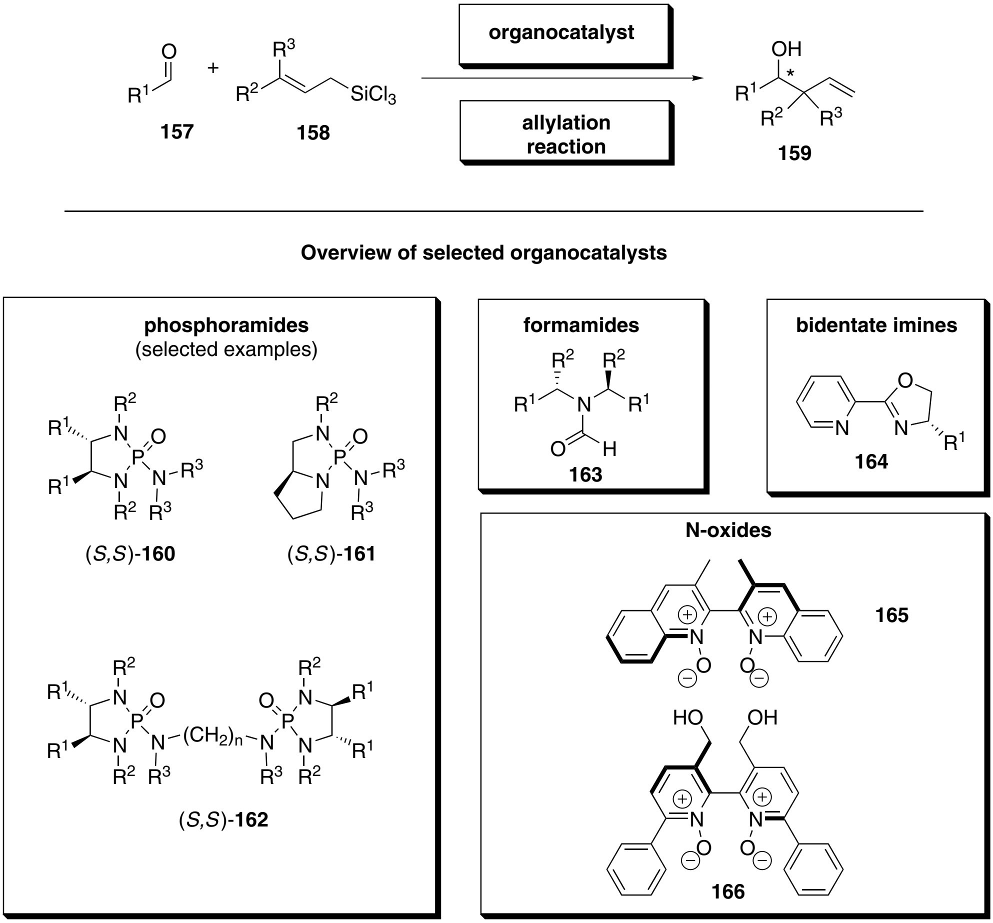
6.5 Allylation Reactions

The enantioselective allylation of aldehydes is another C–C bond-forming reaction of wide interest [162]. The resulting unsaturated alcohols are used as versatile intermediates in the construction of many interesting molecules, e.g. natural products. In this connection, the numerous modifications of these homoallylic alcohols are impressive. The "classic" approach in the field of asymmetric catalytic allylation is based on use of an optically active Lewis acid complex [163]. This metal-catalyst activates the electrophilic aldehyde which then undergoes an addition reaction with the nucleophilic allylmetal reagent. The reaction can, however, also be performed by using an organic Lewis-base molecule as a chiral catalyst. The principle of this organocatalytic allylation reaction is shown in Scheme 6.66.

A broad variety of organocatalyst has been found to catalyze the enantioselective allylation of aldehydes. An overview of the type of organocatalyst successfully applied is also given in Scheme 6.66. The range of organocatalyst developed by numerous groups comprises optically active phosphoramides, formamides, imines, and *N*-oxides. The scope and limitations of those catalysts differ remarkably, in particular with regard to enantioselectivity. Among these, however, are several organocatalysts, in particular phosphoramides, formamides, and *N*-oxides, which catalyze the allylation reaction highly enantioselectively, and tolerate a wide range of substrates. The different types of organocatalytic allylation reaction are described in more detail below.

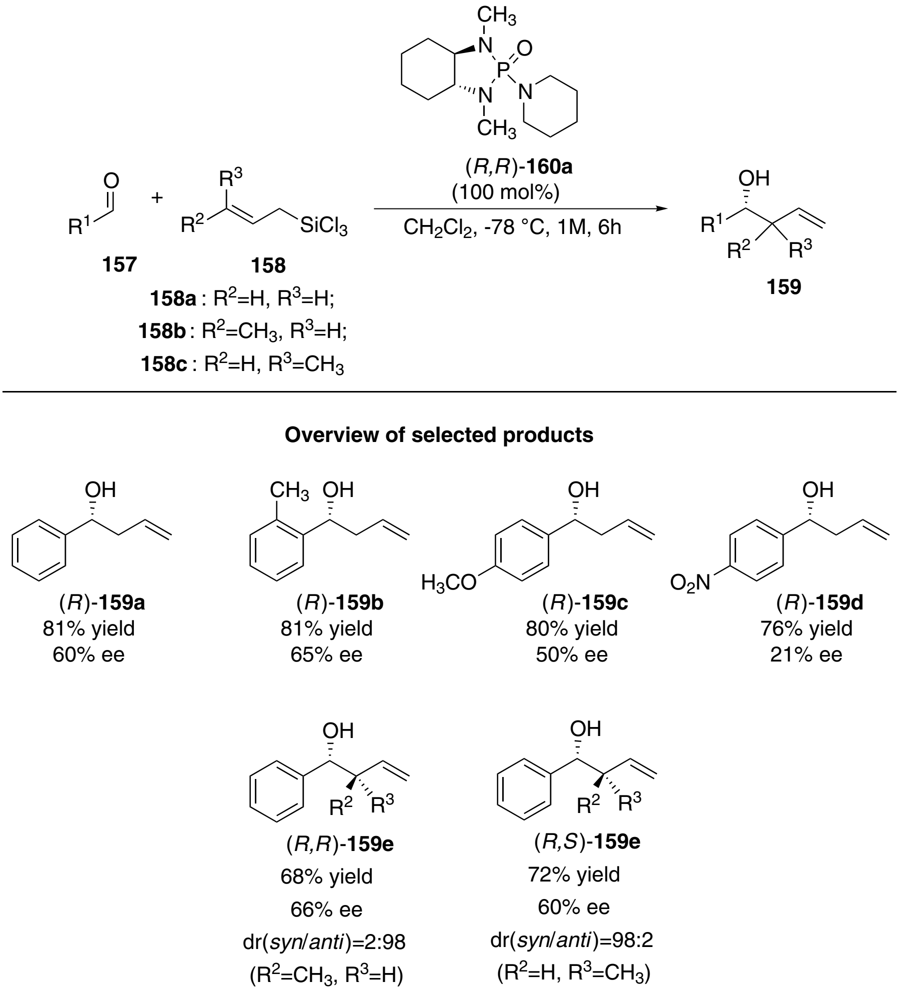
6.5.1 Chiral Phosphoramides as Organocatalysts

The phosphoramide-catalyzed allylation of aldehydes is probably the most intensively investigated organocatalytic allylation reaction to date [164]. The first exam-



Scheme 6.66

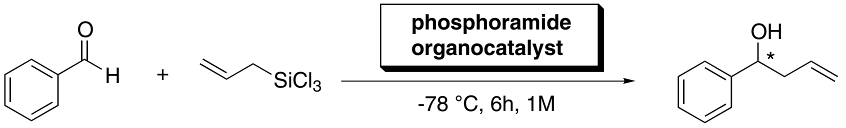
ple of this reaction – which was also the first Lewis-base catalyzed allylation – was reported in 1994 by the Denmark group [165]. Screening of several achiral Lewis bases showed that the phosphoramide HMPA efficiently catalyzes the allylation of benzaldehyde. Subsequent investigation of optically active phosphoramides revealed that the Lewis base (*R*,*R*)-**160a** is an efficient organocatalyst which also accepts a broad range of substrates. Use of allyltrichlorosilane, **158a**, as nucleophile and aldehydes **157** in the presence of (*R*,*R*)-**160a** led to the desired products of type **159a–d** in yields of up to 81% and enantioselectivity up to 65% ee (Scheme 6.67). Although for these reactions the catalyst was used in stoichiometric amounts, the reaction can also be conducted in the presence of catalytic amounts. This has been demonstrated for allylation of benzaldehyde. With a catalytic amount of at least 25 mol% (*R*,*R*)-**160a** comparable yields and enantioselectivity can be achieved.



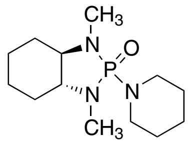
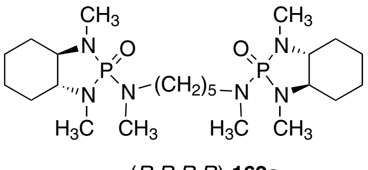
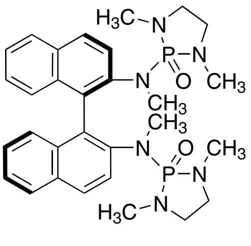
Scheme 6.67

Substituted allyltrichlorosilanes can also be used, resulting in a diastereo- and enantioselective reaction. This has been shown for crotylations of benzaldehyde with (*E*)- and (*Z*)-propenyltrichlorosilanes, **158b** and **158c**, respectively, resulting in the formation of the products (*R*,*R*)-**159e** and (*R*,*S*)-**159e** (Scheme 6.67) [165]. Excellent diastereoselectivity, with diastereomeric ratio of d.r. = 98:2, was observed for these transformations. The sense of diastereoselective induction depends on the geometry of the allylsilane. Thus, anti diastereomers are obtained preferentially from the (*E*)-substrate **158b** whereas the syn diastereomer is the major diastereomer when the (*Z*)-substrate, **158c**, is used. The yields of the products (*R*,*R*)-**159e** and (*R*,*S*)-**159e** were in the range 68–72% and enantioselectivity was 66 and 60% ee, respectively (Scheme 6.67).

Improvement of the structure of the catalyst was achieved by use of related bisphosphoramides of type **162a** bearing a pentamethylene tether capable of chelation with silicon in the transition structure. These findings were based on clarification of the reaction mechanism (details are given below) [166]. In the presence of 10 mol% (*R*,*R*,*R*,*R*)-**162a** a yield of 54% and enantioselectivity of 72% ee were obtained (Scheme 6.68). In contrast with the monomeric species (*R*,*R*)-**160a** enantioselectivity increased as the amount of catalyst was reduced (for comparison, 65% ee were obtained with 50 mol%). A further breakthrough was achieved by applying the bisphosphoramide (*R*)-**167** bearing a binaphthyldiamine linker. In the presence



157a **158a** **159a**

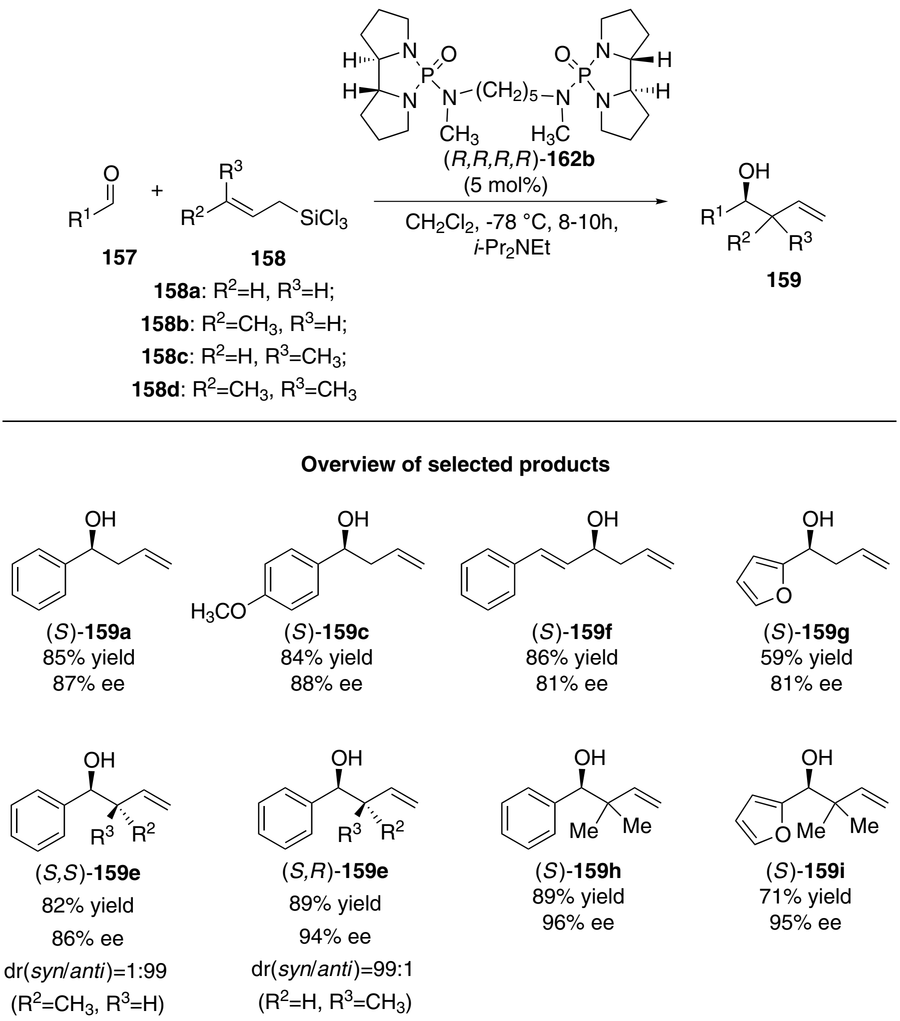
Type of phosphoramide	Cat. amount [mol%]	Yield of **159a** [%]	ee of **159a** [%]
 (*R*,*R*)-**160a**	100	81	60
	50 a)	78	57
	10 a)	40	53
 (*R*,*R*,*R*,*R*)-**162a**	50	78	65
	10	54	72
 (*R*)-**167**	50 b)	76	80
	10 b)	67	80
	5 b)	43	79

a) reaction time was 24h; b) 5 equiv. of *i*-Pr_2EtN was added.

Scheme 6.68

of 10 and 50 mol% of (*R*)-**167** as catalyst enantioselectivity of 80% was obtained (Scheme 6.68). The yield was somewhat higher (76%) if 50 mol% was used, compared with 67% for use of 10 mol%, and even if the amount of catalyst was 5 mol% enantioselectivity remained similar – 79% (yield 43%).

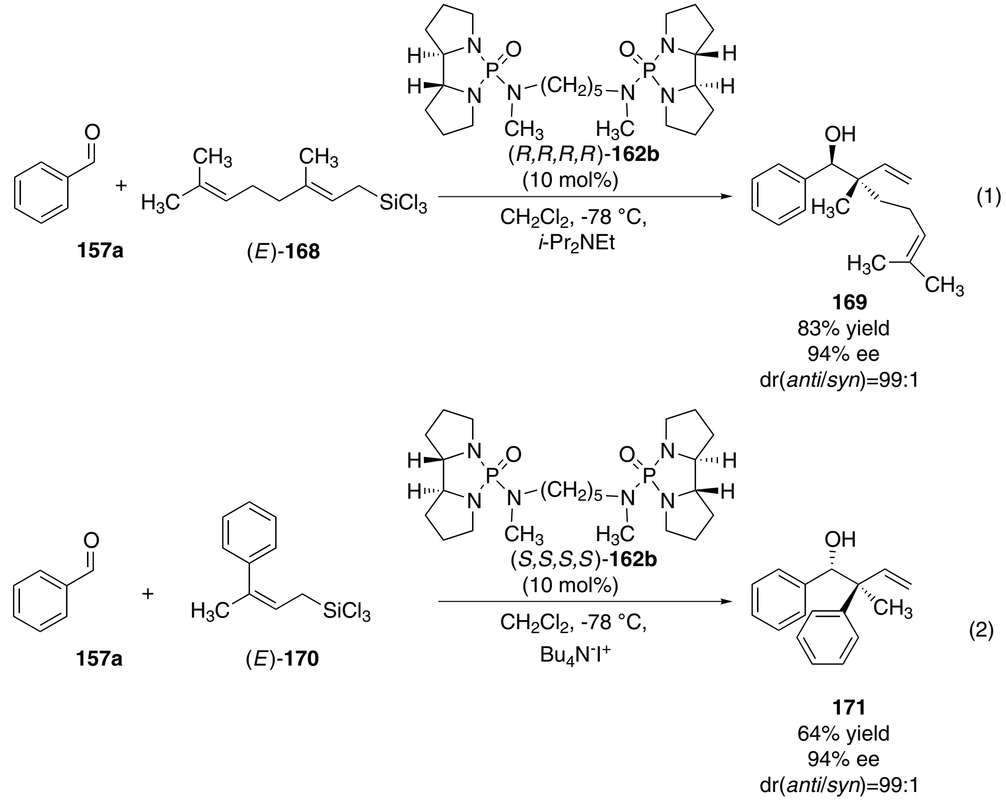
Finally, the jump from satisfactory and good enantioselectivity to excellent ee values was realized by Denmark and co-workers as a result of the development and application of the 2,2′-bispyrrolidine-based bisphosphoramide, (*R,R,R,R*)-**162b**, which also bears a pentamethylene tether [167]. As shown in Scheme 6.69, the allylation can be successfully performed with a broad range of aldehydes **157**, and allyltrichlorosilanes **158**, furnishing the desired products, **159**, in high yields and



Scheme 6.69

with excellent diastereo- and enantioselectivity (Scheme 6.69). Thus, diastereomeric ratio of d.r. = 99:1 was achieved and enantioselectivity was in the range 80–96% ee. Several types of aromatic molecule and cinnamylaldehyde can be used as the aldehyde. In accordance with use of the previously described catalyst (*R*,*R*)-**160a** (Scheme 6.67), the anti and syn diastereomers are produced as the major diastereomers by use of the (*E*)- and (*Z*)-substituted allylic trichlorosilanes, **158b** and **158c**, respectively [167].

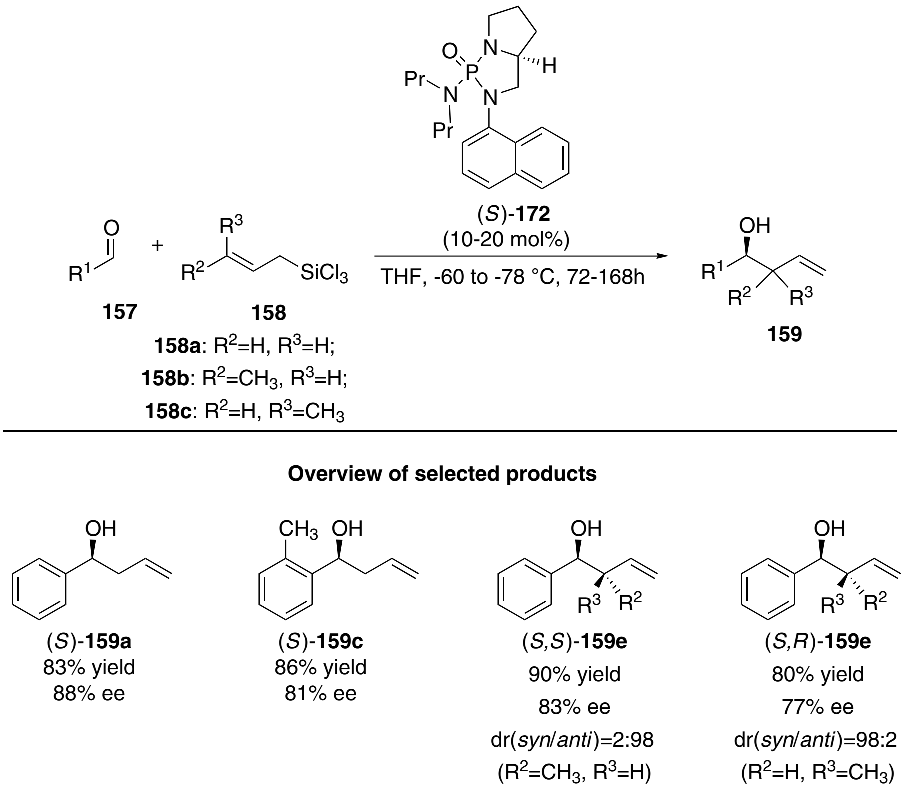
The Denmark-allylation concept can be also used to construct stereogenic quaternary centers [167, 168], as exemplified by the preparation of **169** starting from the (*E*)-geraniol derivative **168** (Scheme 6.70, Eq. 1). The resulting *anti* product **169** was obtained in 83% yield with a diastereomeric ratio of d.r. (anti/syn) = 99/1 and with 94% ee [167]. The potential of the Denmark allylation concept in the construction of chiral quaternary carbon centers has also been impressively demonstrated in the synthesis of **171**, an intermediate in the synthesis of the serotonin antagonist LY426965. The key step is diastereo- and enantioselective allylation of benzaldehyde by use of the (*E*) trichlorosilane **170** in the presence of 10 mol% of the optimized Lewis-base organocatalyst (*S*,*S*,*S*,*S*)-**162b**. The desired anti product



Scheme 6.70

171 bearing a quaternary carbon center was obtained in 64% yield and with a diastereomeric ratio of d.r. (anti/syn) = 99:1 (Scheme 6.70, Eq. 2) [168]. High enantioselectivity, 94% ee, was also observed. The presence of tetra-*n*-butylammonium iodide was found to slightly improve the yield.

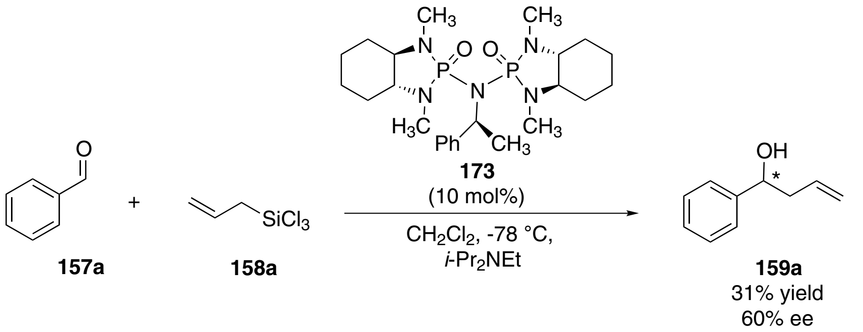
In addition to the Denmark-type organocatalysts, several useful phosphoramides have been developed by other groups [170–172]. The Iseki group constructed (*S*)-proline-derived phosphoramides of type **172** which catalyze the allylation of aromatic aldehydes with high diastereoselectivity and good enantioselectivity of up to 88% ee (Scheme 6.71) [170, 171]. The reactions were conducted in THF – found to be the most suitable solvent – at −78 or −60 °C in the presence of a catalytic amount (10–20 mol%) of **172** [171]. A large excess of the allylic trichlorosilane was used, however, and long reaction times (72–168 h) were required. The highest enantioselectivity of 88% ee was obtained in the allylation of benzaldehyde [170]. When (*E*)- and (*Z*)-crotylsilane **158b** and **158c** were used as substrates the resulting anti and syn products (*S*,*S*)-**159e** and (*S*,*R*)-**159e**, respectively, were formed with excellent diastereoselectivity. The enantiomeric excess of the major diastereomers was also high (77–83% ee). A related phosphoramide bearing a tetrahydro-1-naphthyl group as *N*-substituent (instead of the naphthyl moiety in



Scheme 6.71

(*S*)-**172**) was used at a level of only 1 mol% in the allylation of benzaldehyde and gave the product (*S*)-**159a** in 98% yield and 88% ee; the reaction time was very long, however (336 h) [171].

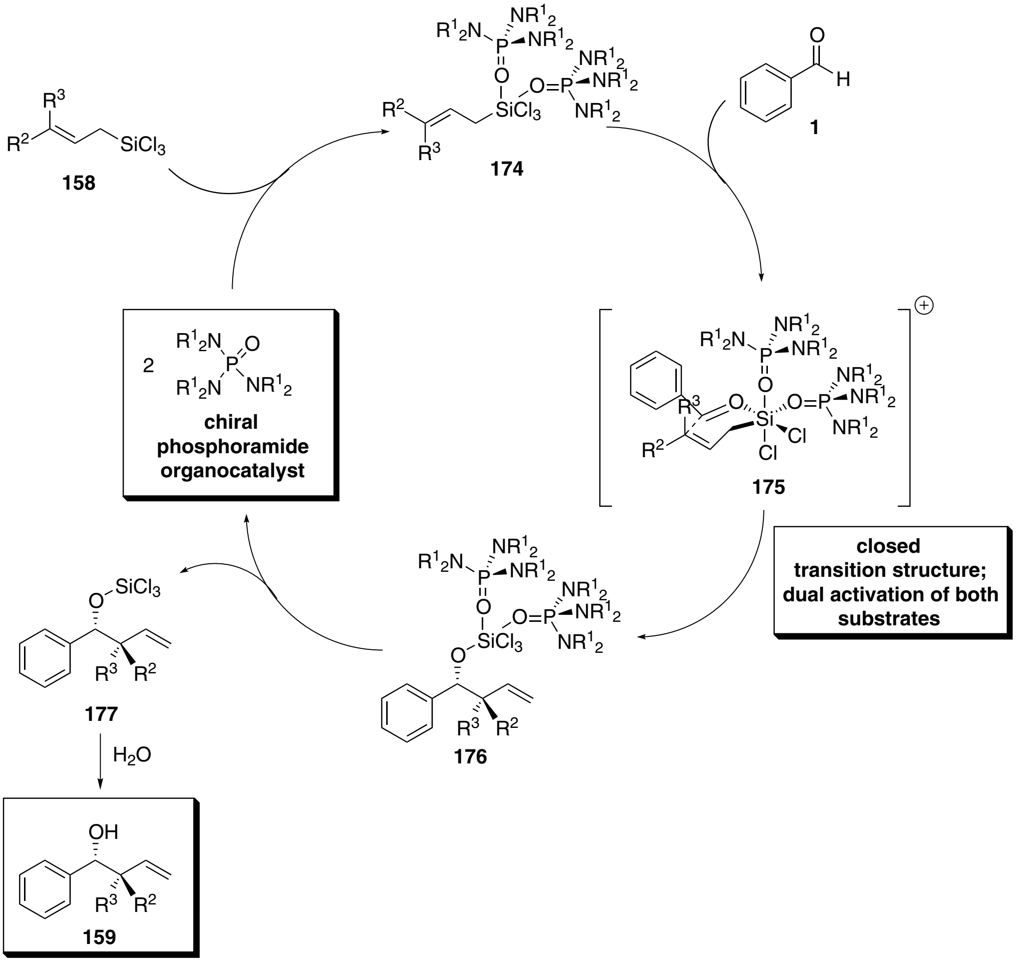
Imidophosphoramides of type **173** are another class of chiral phosphoramide bidentate Lewis base catalyst. These compounds, which are based on the use of primary amines as bridging units, were recently synthesized and applied by the Müller group in an allylation reaction (Scheme 6.72) [172]. Allylation of benzaldehyde with the trichlorosilane **158a** was chosen as model reaction. The catalyst **173** was found to be the most enantioselective, although the yield was low (31%). Other catalysts with a different substitution pattern gave higher yields but also lower enantioselectivity – in the range 18–49% ee. A representative example is shown in Scheme 6.72.



Scheme 6.72

The mechanistic course of the phosphoramide-catalyzed allylation reaction has been investigated in detail, particularly by the Denmark group [164, 166, 169]. An overview of the mechanism is given in Scheme 6.73. A key step is the binding of the nucleophilic allylsilane with the Lewis-base catalyst to form a reactive (hypercoordinate) silicon species, **174**. This intermediate then reacts with the electrophilic aldehyde furnishing the desired homoallylic alcohol product. It is worth noting that the aldehyde is also coordinated to the silicon intermediate. Thus, both substrates are coordinated, and the reaction can proceed through a closed assembly, **175**, of both substrates and two molecules of the catalyst; this is of benefit in ensuring a highly stereoselective reaction. This mechanism of dual activation led to high diastereo- and enantioselectivity.

The higher efficiency of the bisphosphoramides has been also rationalized by the Denmark group on the basis of this mechanism [166]. The improved enantioselectivity can be explained in terms of the increased effective concentration of the second phosphoramide moiety as a result of the intramolecular linkage. This leads to the preferred formation of highly stereoselective assemblies of type **175** which contain two phosphoramide moieties (connected *via* the linker). With the latter the formation of competing, less stereoselective assemblies bearing only one phos-



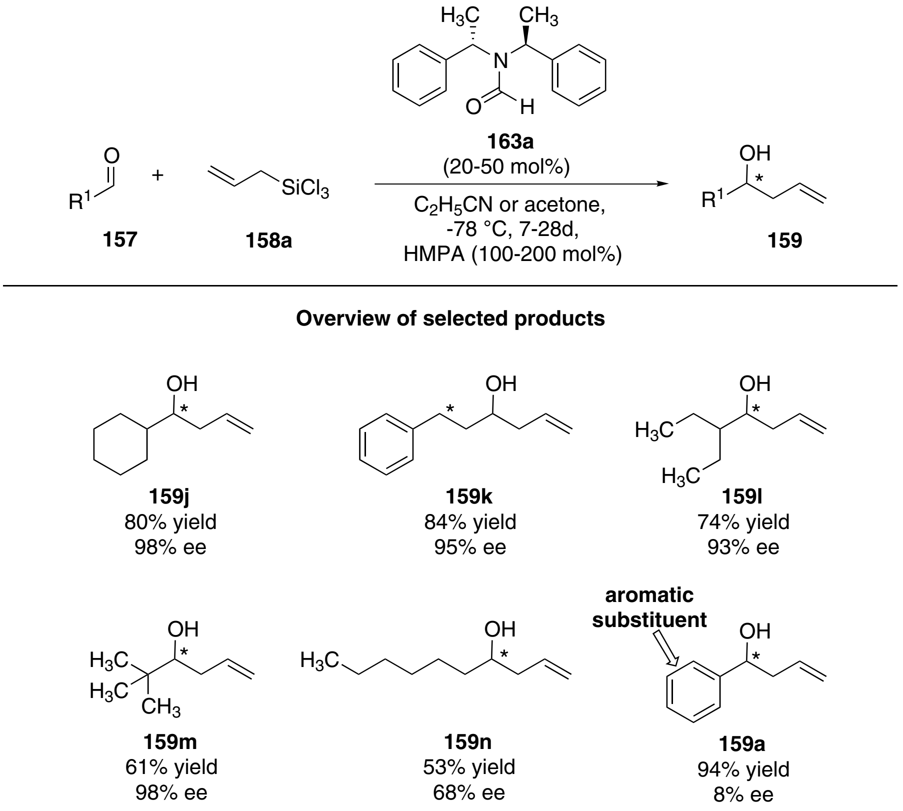
Scheme 6.73

phoramide group is more likely; this leads to lower stereoselectivity when using monophosphoramides. Very recently, Denmark and co-workers reported solution NMR spectroscopic studies and X-ray crystallographic data which supported this mechanism and also provided insight into the transition structure assembly [169].

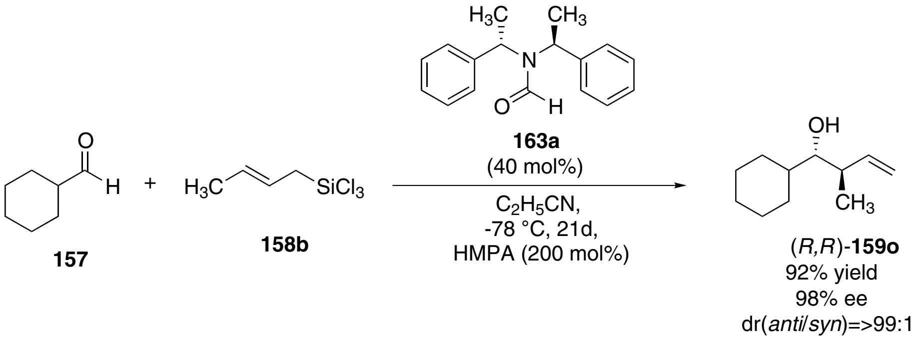
6.5.2 Chiral Formamides as Organocatalysts

In addition to phosphoramide-based organocatalysts, chiral C_2-symmetric formamides were found to be versatile catalysts the asymmetric allylation of alde-

hydes [173, 174]. Interestingly, this organocatalytic approach was found to be complementary to the phosphoramide-catalyzed allylation with regard to substrate range. Whereas aromatic aldehydes were very well tolerated as substrates, phosphoramide-catalyzed allylation of aliphatic aldehydes resulted in poor enantioselectivity. For allylation of such substrates the Izeki group developed a suitable formamide-based organocatalyst, **163a**. The addition of allyltrichlorosilane, **158a**, to cyclohexylcarboxaldehyde with formation of product **159j** was chosen as model reaction. Screening of several C_2-symmetric chiral formamides revealed that the formamide **163a** was the most efficient organocatalyst [174]. For high enantioselectivity the use of a stoichiometric amount of HMPA as additive is essential. An overview of the substrate range is given in Scheme 6.74. In the presence of 20 mol% organocatalyst **163a** and 100–200 mol% HMPA allylation of cyclohexylcarboxaldehyde gave the product **159j** in 80% yield and with excellent enantioselectivity (98% ee) [173]. High enantioselectivity was also obtained by use of other aliphatic aldehydes (Scheme 6.74). Pivaldehyde, for example, was converted into the product **159m** in 61% yield and with 98% ee. Much lower enantioselectivity was, however, observed if straight-chain substrates were used (see, e.g., **159n**) and use of benzal-



Scheme 6.74



Scheme 6.75

dehyde resulted in formation of **159a** with only 8% ee, emphasizing that catalyst **163a** is suitable for aliphatic substrates but is not efficient for aromatic aldehydes.

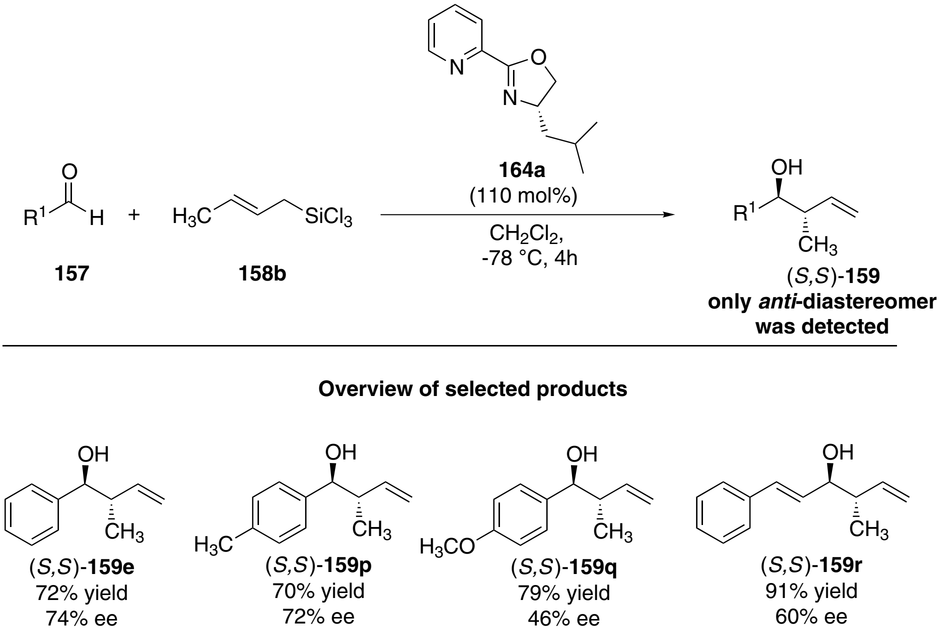
Crotylation of aldehydes with (*E*)- and (*Z*)-crotyltrichlorosilane was also investigated. In the presence of 40 mol% of **163a** allylation with (*E*)-crotyltrichlorosilane, **158b**, was highly diastereo- and enantioselective. High diastereoselectivity with a d.r. (anti/syn) ratio of >99:1 and enantioselectivity up to 98% ee for the major diastereomer have been observed [174]. Yields are also high – up to 97%. A current drawback is, however, the long reaction time of 3 weeks. A representative example is shown in Scheme 6.75. In contrast, a low yield of 19% is obtained, even after reaction for 3 weeks, when the corresponding (*Z*)-crotyltrichlorosilane is used, and diastereoselectivity is only moderate (d.r. (anti/syn) = 60:40). Enantioselectivity for the anti product is, however, still high (98% ee).

6.5.3
Chiral Pyridine Derivatives as Organocatalysts

On the basis of their observation that achiral 2,2′-bipyridyl promotes the reaction between crotyltrichlorosilane and benzaldehyde, the Barrett group screened chiral pyridine molecules as Lewis-base catalysts for this reaction [175]. The pyridinyloxazoline **164a** was identified as the most efficient organocatalyst. In the presence of this catalyst, which was, however, used in stoichiometric amounts, asymmetric addition of (*E*)-crotyltrichlorosilane **158b** to aldehydes gave the anti products (*S*,*S*)-**159** in yields of 61–91% and with enantioselectivity from 36 to 74% ee (Scheme 6.76) [175]. Diastereoselectivity is high, because only the anti diastereomers were obtained. Aromatic aldehydes and cinnamylaldehyde were used as substrates.

6.5.4
Chiral *N*-Oxides as Organocatalysts

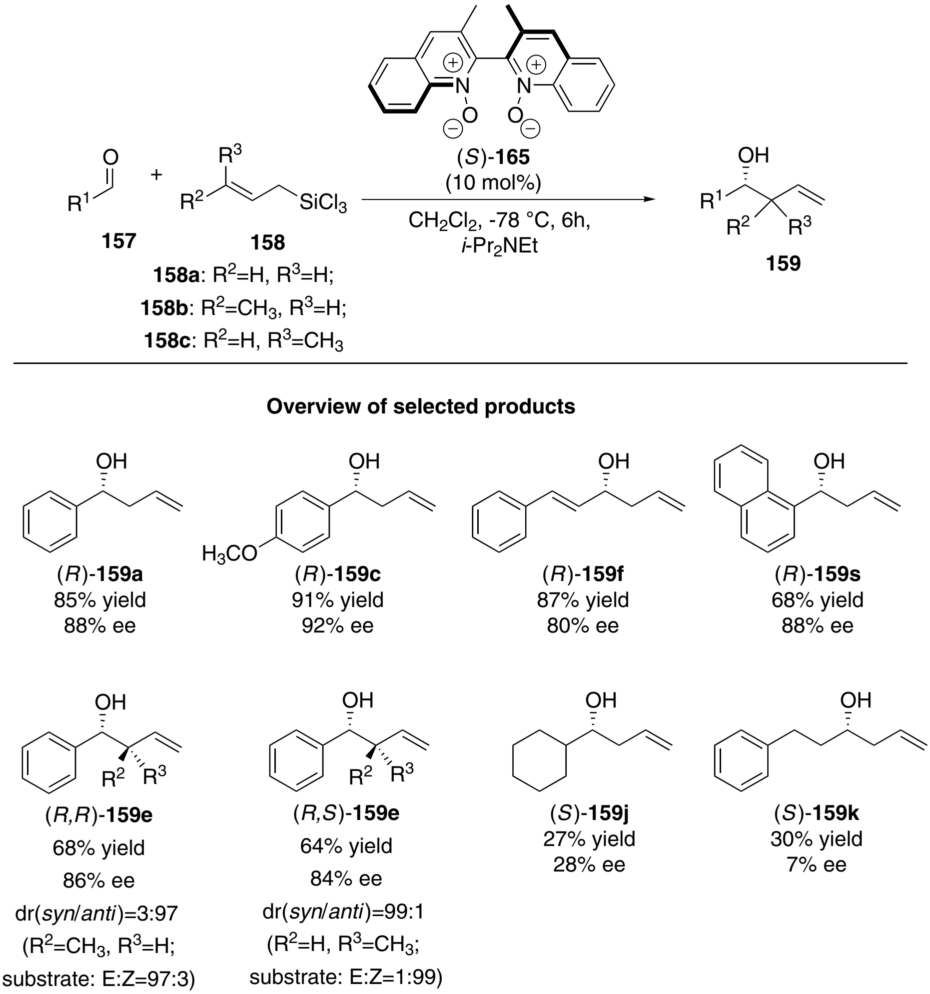
The suitability of a different type of organocatalyst, chiral *N*-oxides, for asymmetric allylation was discovered by the Nakajima group [176]. On the basis of the knowl-



Scheme 6.76

edge that amine *N*-oxides have significant nucleophilicity toward the silicon atom [177], Nakajima and co-workers focused on the development of chiral amine *N*-oxide derivatives which can function as organocatalysts in asymmetric allylation [176]. (*S*)-3,3′-Dimethyl-2,2′-biquinoline *N*,*N*′-dioxide, (*S*)-**165**, was identified as an optimized Lewis-base catalyst. Under optimized reaction conditions a broad range of aromatic and aliphatic aldehydes and α,β-unsaturated aldehydes were allylated with allylic trichlorosilane in the presence of a catalytic amount (10 mol%) of (*S*)-**165**. Good to high yields and enantioselectivity in the range 71–92% ee were usually obtained when aromatic aldehydes were used (Scheme 6.77) [176]. Use of α,β-unsaturated aldehydes also led to good enantioselectivity of 80 to 81% ee whereas both low yields and enantioselectivity were obtained for use of aliphatic aldehydes. Thus, by analogy with the phosphoramide Lewis-base catalysts, e.g. type **162**, aromatic aldehydes are preferred substrates for the chiral *N*-oxide organocatalyst (*S*)-**165**. An overview of the substrate range is given in Scheme 6.77.

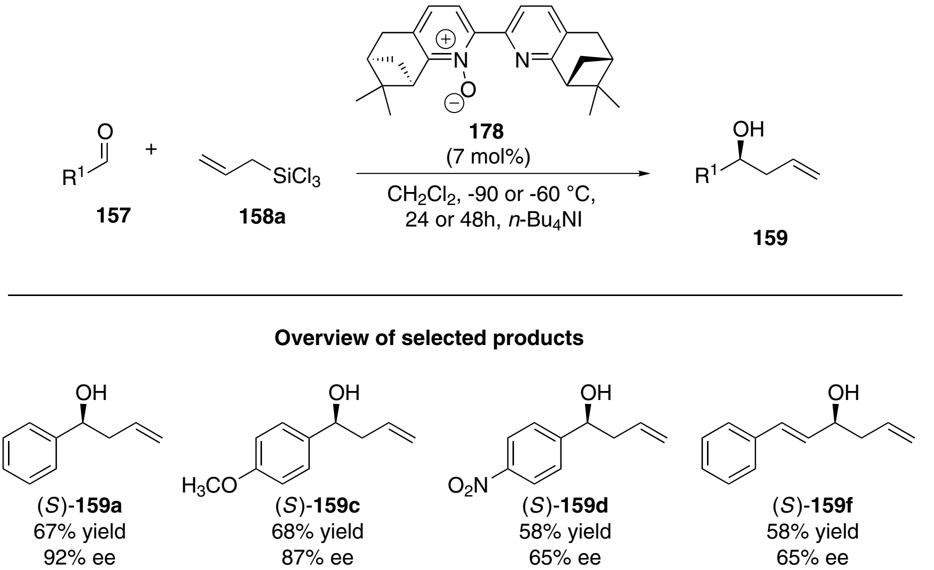
Use of diisopropylethylamine as an achiral additive was found to be beneficial, because of remarkable acceleration of the rate of the reaction. Although enantioselectivity was comparable in the presence or absence of this additive, the acceleration enabled the reaction to be conducted at low temperature which improved the asymmetric induction. Interestingly, amines other than diisopropylethylamine did not give satisfactory results. It is also worthy of note that the reaction time is short with 6 h only.



Scheme 6.77

Chiral *N*-oxides of type (*S*)-**165** can be also used for diastereo- and enantioselective allylation using (*E*)- and (*Z*)-crotyltrichlorosilanes [176]. For these substrates, high diastereoselectivity led to the anti-diastereomer when (*E*)-crotyltrichlorosilane, **158b**, was used and the syn-diastereomer when the (*Z*)-substrate, **158c**, was used (Scheme 6.77). For example, formation of the anti-diastereomer (*R*,*R*)-**159e** proceeded with 68% yield and excellent diastereoselectivity of d.r. (syn/anti) = 3:97. Enantiomeric excess for the major anti-diastereomer (*R*,*R*)-**159e** was 86%.

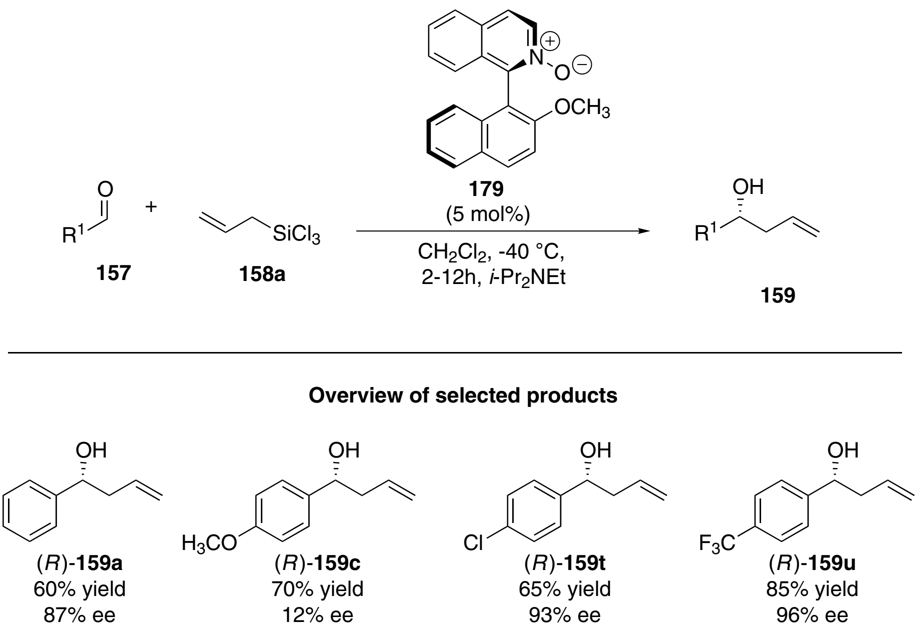
A related *N*-oxide organocatalyst of type **178**, developed by Malkov and Kocovsky et al., has been used for successful asymmetric allylation of aldehydes [178]. It is worthy of note that the corresponding *N*,*N'*-dioxide gave less satisfactory results. In the presence of 7 mol% *N*-monoxide **178**, aromatic aldehydes have been con-



Scheme 6.78

verted with good to high enantioselectivity of up to 92% ee. Yields were moderate for most of the substrates. Selected examples are shown in Scheme 6.78. In contrast with the good results for aromatic substrates use of the aliphatic aldehyde cyclohexylaldehyde led to substantially lower yield (ca. 10%) and enantioselectivity (4% ee).

It has also been found there is no need for the second nitrogen in **178** to obtain high enantioselectivity [179, 180]. Replacing the pyridyl subunit in **178** by phenyl or substituted analogs thereof also led to asymmetric induction, although the type of substituent has an effect on the enantioselectivity [179]. This observation led to the conclusion that arene–arene interactions (π-stacking) of the aromatic aldehyde substrate and the phenyl subunit might be involved in the reaction. Because these interactions would be affected by the pattern of substitution on the phenyl group, fine-tuning of the catalyst should be possible by modifying these substituents. This has been confirmed by using isoquinoline *N*-oxide catalyst **179**, which contains an electron-rich *o*-methoxyphenyl subunit, for asymmetric allylation of electron-poor aromatic substrates [180]. As expected, high enantioselectivity was obtained in the allylation of electron-poor benzaldehydes, as is shown representatively in Scheme 6.79 for synthesis of (*R*)-**159t** and (*R*)-**159u** with 93 and 96% ee, respectively [180]. In contrast, electron-rich aromatic substrates gave almost racemic products. A selected example is product (*R*)-**159c**, which was obtained with 12% ee only. Because modest enantioselectivity only has previously been reported for allylation of electron-poor benzaldehydes, this method based on catalyst **179** is the first highly enantioselective allylation of this type of substrate. The amount of catalyst can be

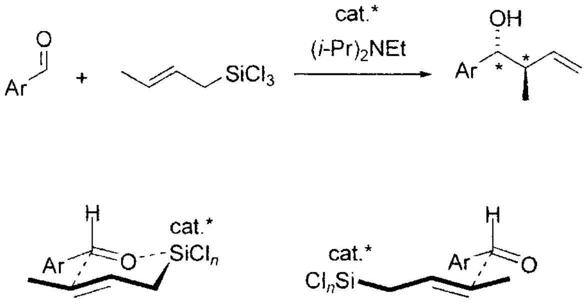


Scheme 6.79

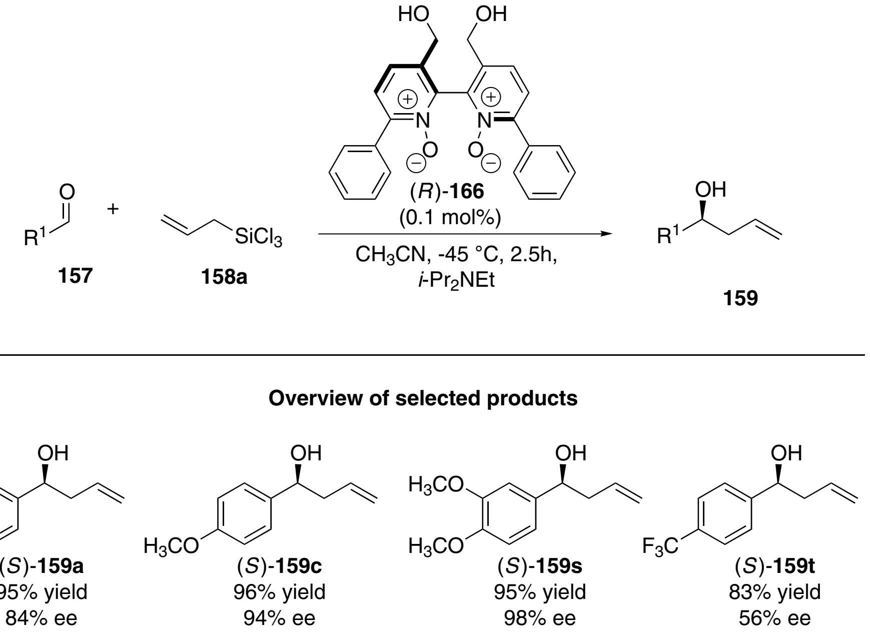
reduced from 5 mol% to 1 mol% without loss of enantioselectivity, albeit at the expense of longer reaction times (12 h rather than 2 h).

This reaction has also been applied to enantio- and diastereoselective synthesis using *trans*-crotyltrichlorosilane as substrate [180]. Once again, the highest enantioselectivity was observed for electron-poor benzaldehydes. Interestingly, however, diastereoselectivity was lower than for benzaldehyde. One explanation is that for catalyst **179** the preferred cyclic transition state leading to the major anti products is less favored as arene–arene interactions become stronger (Scheme 6.80) [180]. Stronger arene–arene interactions result in increased participation of the open-chain transition state, and reduced diastereoselectivity.

Impressive reduction of the amount of catalyst used has recently been reported by the Hayashi group [181]. Use of very small amounts (< 1 mol%) of *N*-oxide organocatalysts of type **166** gave excellent results. In the presence of only 0.1 mol% **166** allylation of several aromatic aldehydes proceeds with formation of the desired products **159** with high enantioselectivity – up to 98% ee (Scheme 6.81). Only for *p*-trifluoromethylbenzaldehyde medium enantioselectivity (56% ee) was observed. Electron-donating substituents of the benzaldehyde usually had a beneficial effect. Yields also are usually high (83–96%). It is also worthy of note that the reaction time is very short – 2.5 h only. As has been demonstrated for the product (*S*)-**159c**, the amount of catalyst can be further reduced from 0.1 mol% to 0.01 mol% without loss of enantioselectivity, although the reaction time increased from 2.5



Scheme 6.80 (from Ref. 180)



Scheme 6.81

to 12 h and the yield was somewhat lower (68%, compared to 96% for 0.1 mol% catalyst).

Conclusion

Enantioselective allylation of aldehydes catalyzed by chiral organocatalysts has reached a high state of the art. Since the first report by the Denmark group in 1994 this organocatalytic approach has been developed toward an advanced and efficient method for preparation of the corresponding target molecules. In addition to the high enantio- and diastereoselectivity obtained, the broad range of useful organocatalysts is particularly worthy of note. The range of organocatalysts developed includes phosphoramides, formamides, pyridine derivatives, and *N*-oxides.

6.6 Alkylation of C=O Double Bonds

Asymmetric catalytic addition of alkyl nucleophiles to carbonyl compounds with formation of optically active secondary and, in particular, tertiary alcohols is still a challenge for organic chemists. An effective catalytic route to tertiary alcohols is asymmetric addition of organometallic nucleophiles to the C=O double bond of ketones in the presence of chiral metal catalysts [182]. Enzymatic resolution of racemic tertiary alcohols, which can be readily prepared *via* Grignard reaction with ketones, is also of importance [183]. Although an efficient asymmetric catalytic Grignard reaction, which would be very attractive, has not yet been realized, the Grignard reaction proceeds well with high enantioselectivity when stoichiometric amounts of the chiral ligand are used [184].

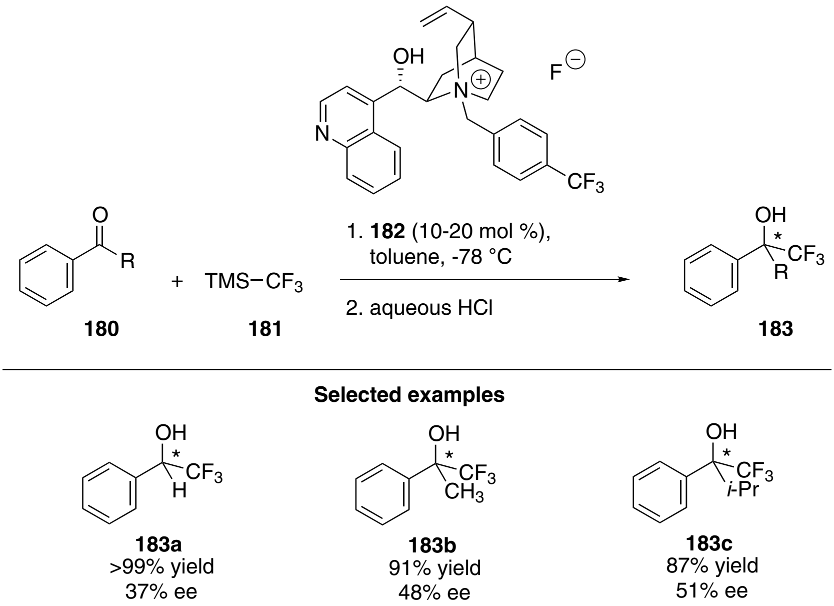
A procedure for alkylation of C=O double bonds in the presence of (metal-free) organocatalysts and non-metallic nucleophiles has been reported by the Iseki group for trifluoromethylation of aldehydes and ketones [185]. On the basis of a previous study of the Olah group [186, 187] which showed the suitability of non-chiral phase-transfer catalysts for trifluoromethylation of carbonyl compounds, Iseki et al. investigated the use of *N*-benzylcinchonium fluoride, **182**, as a chiral catalyst. The reaction has been investigated with several aldehydes and aromatic ketones. Trifluoromethyltrimethylsilane, **181**, was used as nucleophile. The reaction was, typically, performed at −78 °C with a catalytic amount (10–20 mol%) of **182**, followed by subsequent hydrolysis of the siloxy compound and formation of the desired alcohols of type **183** (Scheme 6.82).

When aldehydes were used as substrates excellent yields of at least 98% were obtained after a short reaction time of 2 h only (Scheme 6.82). Enantioselectivity, however, was low to moderate (15–46% ee). Representative examples are shown in Scheme 6.82. Ketones were also used as a carbonyl substrate, and led to the products **183b**,**c** in high yields (up to 91%) and with enantioselectivity of 48–51% ee (i.e., comparable with that obtained for use of aldehydes).

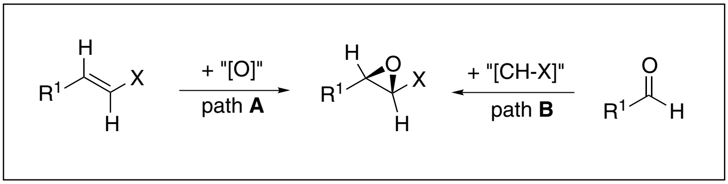
In summary, this organocatalytic alkylation of aldehydes and ketones is a promising route for preparation of optically active secondary and tertiary alcohols and is of general interest. Certainly, improvement of the asymmetric induction as well as applications of other nucleophiles will be the next major challenge in this field to make this synthetic concept competitive with alternative routes.

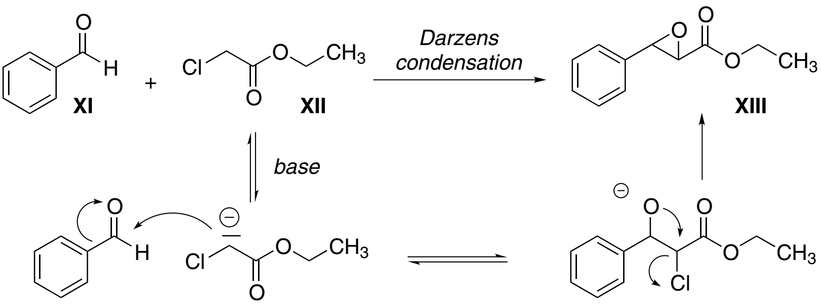
6.7 The Darzens Reaction

The Darzens reaction is the base-promoted generation of epoxides **XIII** from aldehydes (or ketones) **XI** and alkyl halides **XII**, the latter carrying an electron withdrawing group, for example the carbonyl, nitrile, or sulfonyl, in the α-position (Scheme 6.83) [188, 189]. It is, formally, addition of a carbene to the C=O double bond (Scheme 6.83, path **B**) and thus complements oxygen atom transfer to olefins



Scheme 6.82





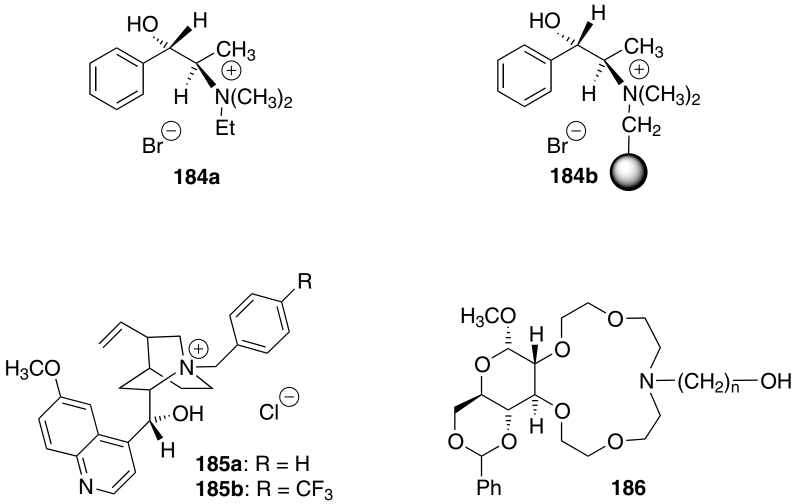
Scheme 6.83

as a method for the synthesis of epoxides (Scheme 6.83, path **A**). As shown in Scheme 6.83, the mechanism of the Darzens condensation involves deprotonation of the C–H acidic halide to form, e.g., an enolate anion. The latter adds to the aldehyde, affording the anion of a *β*-halohydrin which ring-closes to the product epoxide. Obviously, both *E* and *Z* epoxides can result from the Darzens synthesis, and good diastereoselectivity is a prerequisite for synthetically useful processes.

It should be noted that the nucleofugal group in component **XII** (Scheme 6.83) might also be a cationic sulfonium moiety. In this circumstance the nucleophile attacking the aldehyde is a sulfur ylide. Catalytic enantioselective versions of the transformation of aldehydes to epoxides involving sulfur ylides are covered in Section 6.8.

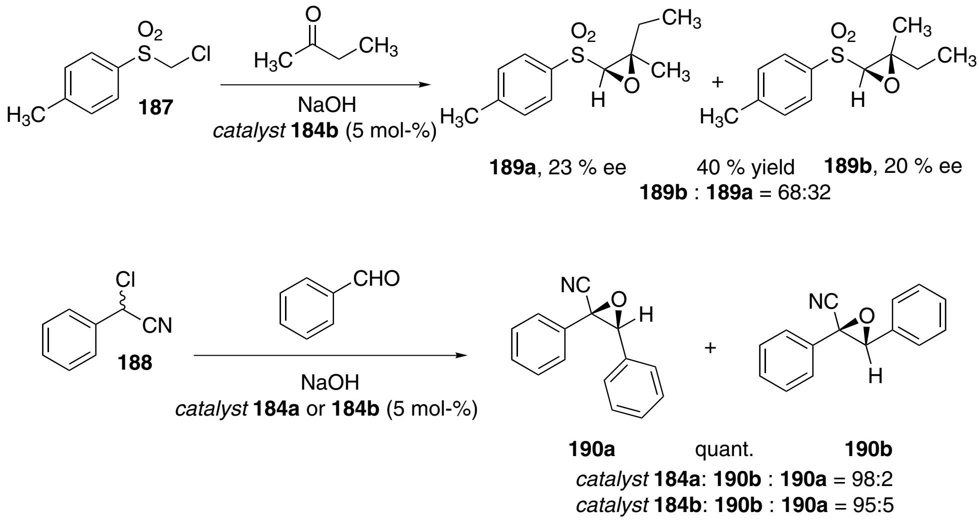
All catalytic enantioselective versions of the Darzens condensation are based on the use of chiral phase-transfer agents, e.g. the cations **184a**,**b** derived from ephedrine, quinine/quinidine-based ammonium ions such as **185a**,**b**, or the crown ether **186**.

Chiral phase-transfer catalysts used in the asymmetric Darzens condensation:



As early as 1978 both the ephedrinium salt **184a** and its solid-phase bound analog **184b** were tested by Colonna et al. in the Darzens condensation of ketones and aldehydes with *para*-tolyl chloromethylsulfone **187** or *α*-chlorophenyl acetonitrile **188** (Scheme 6.84) [190]. Optical yields (< 30%) were reported only for the mixture of the products **189a** and **189b**. For nitriles **190a** and **190b** the *trans* epoxide **190b** was reported as the major diastereomer. The enantiomeric excess of the epoxides **190a** and **190b** could not be determined, unfortunately [190].

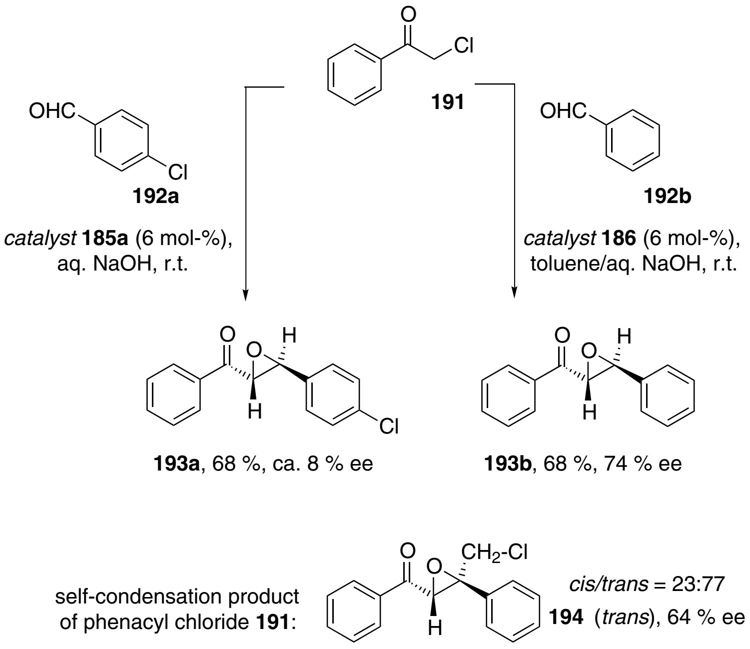
Also in 1978, Wynberg and Hummelen used the benzyl quininium chloride **185a** as a chiral phase-transfer catalyst in the Darzens condensation [191]. In the



Scheme 6.84

reaction of *para*-chlorobenzaldehyde (**192a**) with phenacyl chloride (**191**), the trans chalcone epoxide **193a** was formed in 68% yield and with ca. 8% ee (Scheme 6.85) [191]. Essentially the same transformation (benzaldehyde **192b** instead of *para*-chlorobenzaldehyde **192a**) was reported in 1998 by Töke et al., who used the crown ether phase-transfer catalysts **186** derived from D-glucose [192]. Using the *N*-hydroxypropyl catalyst **186** ($n = 3$), the trans chalcone epoxide **193b** (d.r. > 98:2) was obtained with up to 74% ee (Scheme 6.85) [192b,c]. In the course of their studies Töke et al. observed that part of the phenacylchloride **191** is consumed by self-condensation, affording the epoxyketone **194** with 64% ee of the trans product (Scheme 6.85) [192d]. In a more general sense this result indicates the potential of the Darzens condensation for side-reactions by self-condensation of the chloroketone substrates. Enantiomerically enriched dimerization products such as **194** are also interesting building blocks.

Significantly improved enantioselectivity compared with the Wynberg and Hummelen experiment was achieved by Arai and Shiori by introduction of trifluoromethyl substituents to the benzyl group of the catalyst **185a** [193, 194]. In particular, a *para*-trifluoromethyl group (catalyst **185b**, see above) proved beneficial. For example, in the condensation of phenacyl chloride **191a** with several aliphatic aldehydes **194a–h** and benzaldehyde (**194i**), the trans epoxy ketones **195** were obtained exclusively, and enantiomeric excesses up to 79% were achieved (Table 6.1) [193]. It was found that induction was much lower when the trifluoromethyl group in the catalyst **185b** was exchanged for, e.g., a cyano, nitro, or iodo substituent [193]. Later work by Arai and Shiori et al. included the racemic chloroketones **191b,c** [194]. Again by use of the trifluoromethylated catalyst **185b** enantiomeric excesses of the trans epoxyketones **196** as high as 86% were achieved (Table 6.1) [194].



Scheme 6.85

Similarly, chloromethyl phenyl sulfone (**197**) was coupled with several aromatic aldehydes, **198a–i**, again using the trifluoromethylated phase-transfer catalyst **185b** [195]. As summarized in Table 6.2, the trans epoxysulfones **199a–i** were obtained in good chemical yields and with enantiomeric excesses up to 81% [195]. In this study the effect of further trifluoromethylation of the benzyl residue in the catalyst **185b** was also investigated. *para*-Trifluoromethylation (as in **185b**) proved best; asymmetric induction was significantly lower for both the 2,4- and 3,5-bis-CF_3-derivatives [195, 196].

Later work by Arai and Shiori included other aromatic aldehydes and showed that aliphatic aldehydes afford appreciable ee only in the presence of the additive $Sn(OTf)_2$ (up to 32%), and that the chloromethylsulfone **197** can also be reacted with the ketones **200a**,**b** in the presence of the phase-transfer **185b** (Scheme 6.86) [196]. 4-*tert*-Butylbenzaldehyde (**198e**, Table 6.2) still gave the best ee (81%).

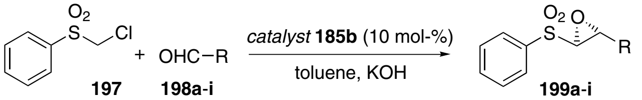
Conclusions

The potential of the Darzens condensation as an alternative means of access to enantiomerically pure epoxy ketones, esters, nitriles, sulfones, etc., has long been recognized. Synthetically useful enantioselectivity was, nevertheless, not achieved until a few years ago when Arai and Shiori introduced the trifluoro-

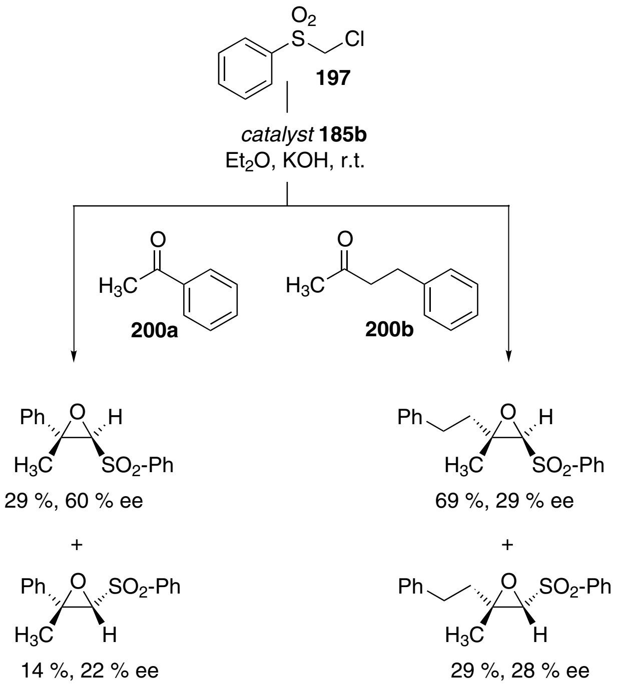
Tab. 6.1

Chloroketone	Aldehyde	R	Yield of 195, 196 [%]	ee [%]	Ref.
191a	**194a**	Et	32	79	193
191a	**194b**	*n*-Pr	82	57	193
rac-**191b**	**194b**	*n*-Pr	67	84	194
191a	**194c**	*i*-Pr	80	53	193
rac-**191b**	**194c**	*i*-Pr	99	69	194
191a	**194d**	*i*-Bu	73	69	193
rac-**191b**	**194d**	*i*-Bu	86	74	194
rac-**191c**	**194d**	*i*-Bu	65	50	194
191a	**194e**	*t*-Bu-CH_2	50	62	193
rac-**191b**	**194e**	*t*-Bu-CH_2	86	86	194
rac-**191c**	**194e**	*t*-Bu-CH_2	90	75	194
191a	**194f**	Et_2CH-CH_2	76	58	192
191a	**194g**	$Ph(CH_2)_2$	83	44	193
191a	**194h**	*c*-Hex	47	63	193
rac-**191b**	**194h**	*c*-Hex	80	69	194
191a	**194i**	Ph	43	42	193

Tab. 6.2



Aldehyde	R	Yield of 199 [%]	ee [%]
198a	Ph	85	69
198b	4-Br-C_6H_4	80	64
198c	3-Br-C_6H_4	69	71
198d	4-Me-C_6H_4	84	78
198e	4-*t*-Bu-C_6H_4	70	81
198f	4-Ph-C_6H_4	71	72
198g	4-PhO-C_6H_4	83	65
198h	3-Me-C_6H_4	82	74
198i	*β*-naphthyl	94	68



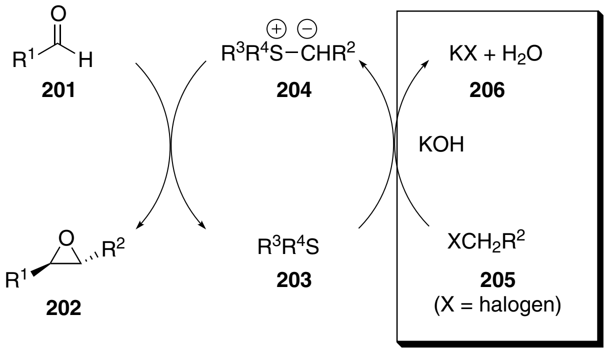
Scheme 6.86

methylated alkaloid-based phase-transfer catalyst **185b** and Töke et al. described the carbohydrate-based chiral crown ethers **186**. Currently, all enantioselective variants of the Darzens condensations are based on the use of chiral phase-transfer catalysts [197]. One of the advantages of the Darzens condensation is that is an experimentally simple process. Because of the current rapid development of novel chiral phase-transfer catalysts, it might be expected that this field will see substantial further growth in the near future.

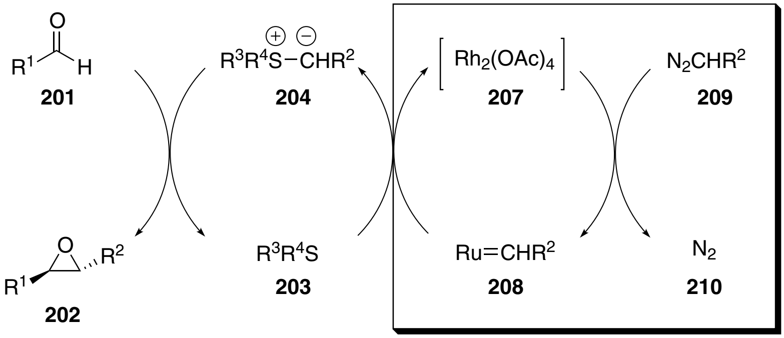
6.8
Sulfur Ylide-based Epoxidation of Aldehydes

Nucleophilic addition of sulfur ylides to C=O double bonds is an important means of synthesis of epoxides [198]. Because optically active epoxides are widely applied as versatile intermediates in the preparation of, e.g., pharmaceuticals, the asymmetric design of this sulfur ylide-based reaction has attracted much interest [199, 200, 212, 213]. One aspect of this asymmetric organocatalytic process which has been realized by several groups is shown in Scheme 6.87A. In the first step a chiral sulfur ylide of type **204** is formed in a nucleophilic substitution reaction starting from a halogenated alkane, a base, and a chiral sulfide of type **203** as organocata-

Concept (A):



Concept (B):



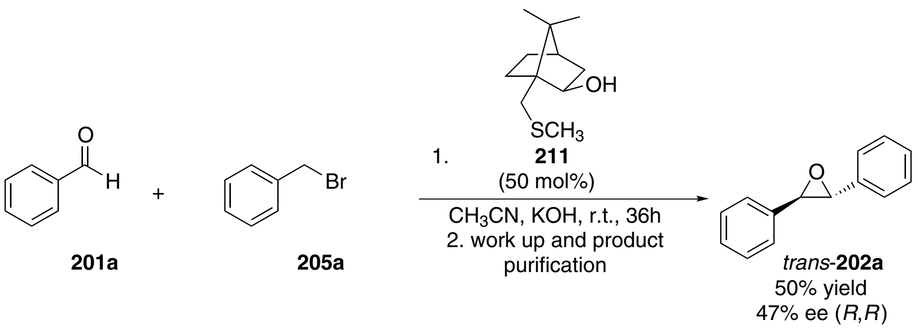
Scheme 6.87

lyst. The chiral ylide **204** then reacts with the carbonyl compound **201** diastereoselectively and enantioselectively with formation of the desired optically active epoxide product **202**. The catalyst is released and can be reused for the next catalytic cycle. This concept based on use of a base for sulfur-ylide formation is described in more detail in the following section.

The sulfur ylide can also be formed by means of a reaction with a diazo compound **209** in the presence of an achiral metal catalyst **207**. This concept, which has a broad range of applications and is of high efficiency, is shown in Scheme 6.87B and will be described in the section from page 219.

6.8.1
Epoxide Formation from Ylides Prepared by Means of Bases

Several chiral sulfides have been found to be suitable organocatalysts for enantioselective epoxidation as illustrated in Scheme 6.87A. An early example was reported by the Furukawa group using sulfides prepared from (+)-camphorsulfonic acid

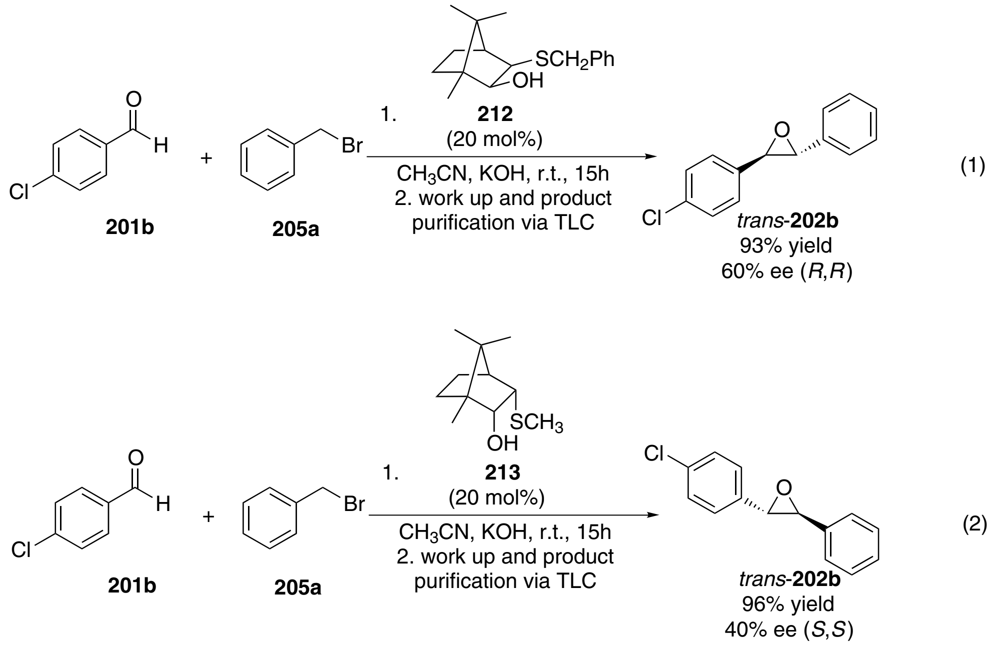


Scheme 6.88

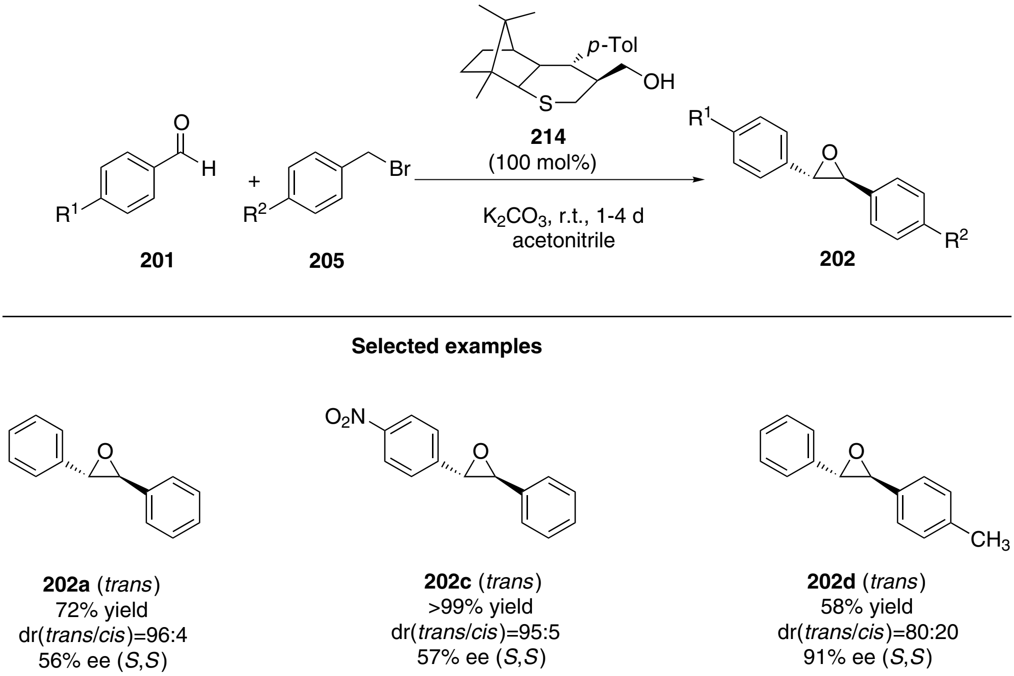
[201, 202]. Screening of different sulfides revealed sulfide **211** was the most promising organocatalyst; acetonitrile was found to be the most suitable solvent. A representative example is shown in Scheme 6.88. In the presence of 50 mol% sulfide **211** and KOH as a base reaction of alkyl halide **205a** with benzaldehyde **201a** furnished the epoxide *trans*-(*R*,*R*)-**202a** in 50% yield and with 47% ee. The reaction can be also performed with other aromatic aldehydes. In general, however, enantioselectivity did not exceed 50% ee irrespective of the substrate.

Improvement of both yield and enantioselectivity was reported by Huang et al., who used, in particular, sulfide **212** derived from D-(+)-camphor as organocatalyst [203]. In addition, only trans products were formed, indicating excellent diastereoselectivity. The reaction proceeded successfully in the presence of 20 mol% catalyst, leading to the epoxide product *trans*-(*R*,*R*)-**202b** in 93% yield and 60% ee (Scheme 6.89, Eq. 1). Other aromatic aldehydes are also suitable substrates. Although the amount of catalyst can be reduced further, longer reaction times are required, yields are reduced, and enantioselectivity is somewhat lower (52–58%) when using only 5 or 10 mol% catalyst [203]. It should be noted that reverse asymmetric induction was achieved by use of, e.g., sulfide **213**, which has an endo methylthio group (Scheme 6.89, Eq. 2), instead of sulfide **212**, which bears an exo benzylthio group [203]. In the reaction using **213**, however, enantioselectivity was somewhat lower. For example, 40% ee was obtained for substrate **201b**, compared with 60% ee when using **212** as organocatalyst in the same reaction. In general, acetonitrile was the preferred solvent, and strong bases were most useful.

The suitability of a new sulfide, **214**, was reported by the Saito group [204]. Screening of solvents revealed that in addition to acetonitrile – which gave the best balance of yield, diastereoselectivity, and enantioselectivity – *tert*-butyl alcohol was the preferred solvent with regard to enantioselectivity for the trans diastereomer. A variety of aromatic substrates and a broad range of different substituents are tolerated. Selected examples are shown in Scheme 6.90. Enantioselectivity was in the range 56–91% ee and high yields – up to >99% – were achieved. Diastereoselectivity was also high – d.r. (trans/cis) ratio up to 95:5. For example, good results were obtained by use of benzaldehyde; the desired trans-product **202d** was obtained in 58% yield and with 91% ee [204]. The reactions also proceeded at



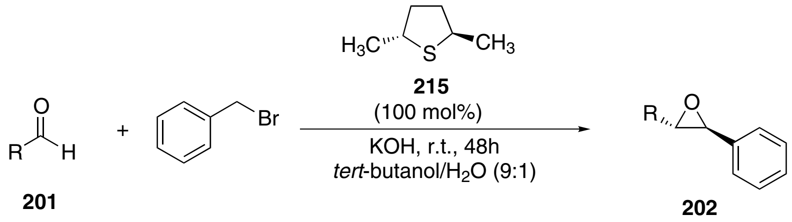
Scheme 6.89



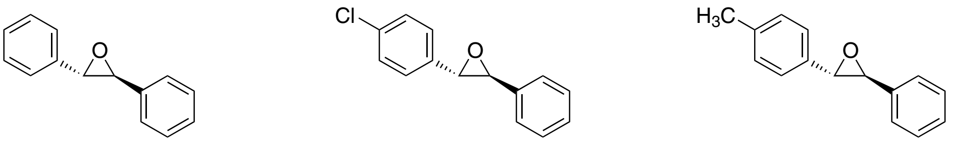
Scheme 6.90

a smaller amount of catalyst, which was steadily reduced from 100 to 10 mol%, although the rate of conversion and the yield were somewhat lower and enantioselectivity decreased slightly. For example, with *p*-nitrobenzaldehyde as a substrate 10 mol% **214** resulted in 48% ee (> 99% yield after 6 days) whereas 57% ee (> 99% yield after 1 day) was obtained when 100 mol% sulfide **214** was used.

The Metzner group focussed on the use of enantiomerically pure *trans*-2,5-dimethylthiolane, **215**, as organocatalyst [205–208]. This chiral sulfide is among the most simple C_2-symmetric sulfides and is readily available in two steps from commercially available (2*S*,5*S*)-hexanediol [206]. During detailed study of the model reaction of benzyl bromide and benzaldehyde furnishing the epoxide (*S*,*S*)-**202a** the reaction conditions were optimized. A 9:1 mixture of *tert*-butanol and water was found to be the optimum solvent with regard to selectivity and yield. In the presence of stoichiometric amounts of the organocatalyst **215** the desired product (*S*,*S*)-**202a** (Scheme 6.91) was synthesized in high yield, 92%, with high diastereoselectivity (d.r. ratio 93:7), and with high enantioselectivity (88% ee) [206]. Under these optimized conditions the range of substrates was investigated [206]. Use of other aromatic substrates also led to high yields, diastereoselectivity, and enantioselectivity (Scheme 6.91). Epoxidation of the unbranched aliphatic aldehyde *n*-pentanal, however, was not successful whereas cyclohexanecarboxaldehyde was converted into the chiral epoxide in 87% yield, and with high enantioselectivity (96% ee), although diastereoselectivity (d.r. ratio 65:35) was somewhat lower than for the aromatic epoxides (*S*,*S*)-**202a,b** [206]. In some epoxidations it was found that the analogous *trans*-2,5-diethylthiolane gave better results [207].



Selected examples



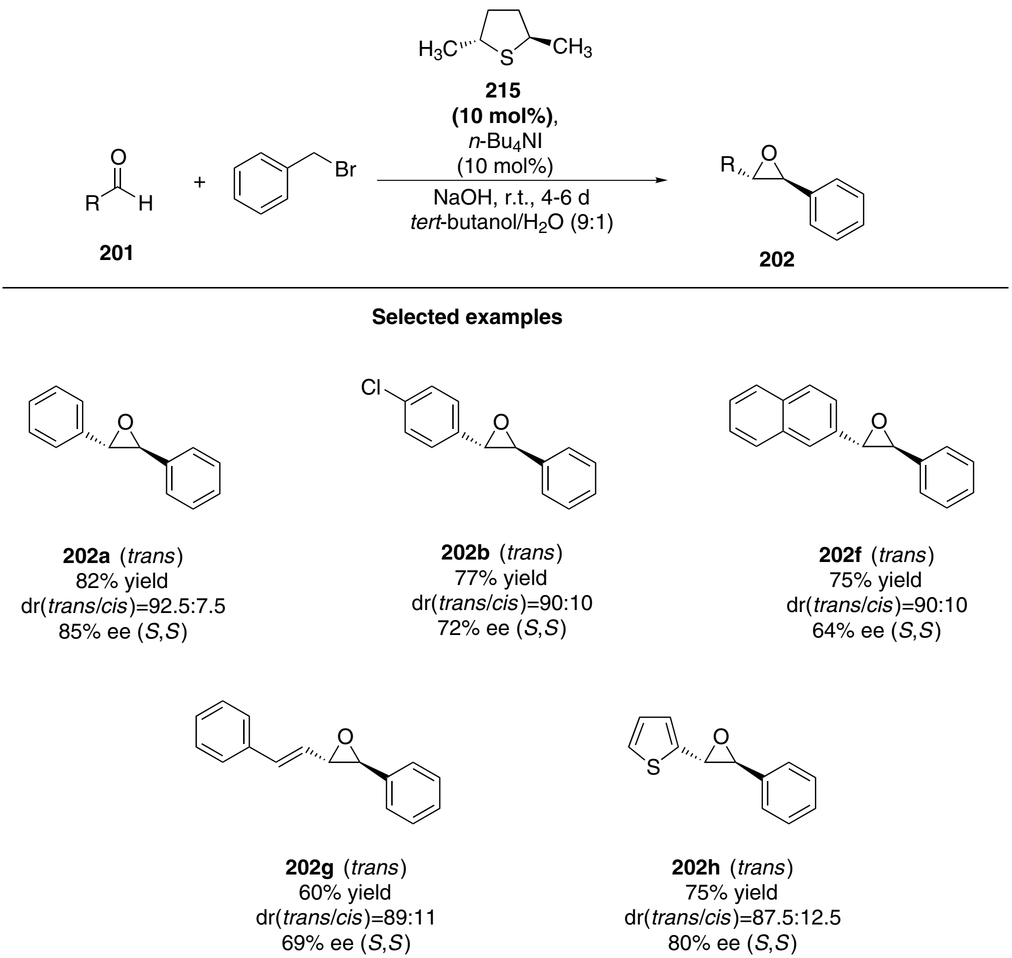
202a (*trans*)
92% yield
dr(*trans*/*cis*)=93:7
88% ee (*S*,*S*)

202b (*trans*)
89% yield
dr(*trans*/*cis*)=92:8
86% ee (*S*,*S*)

202e (*trans*)
88% yield
dr(*trans*/*cis*)=92:8
88% ee (*S*,*S*)

Scheme 6.91

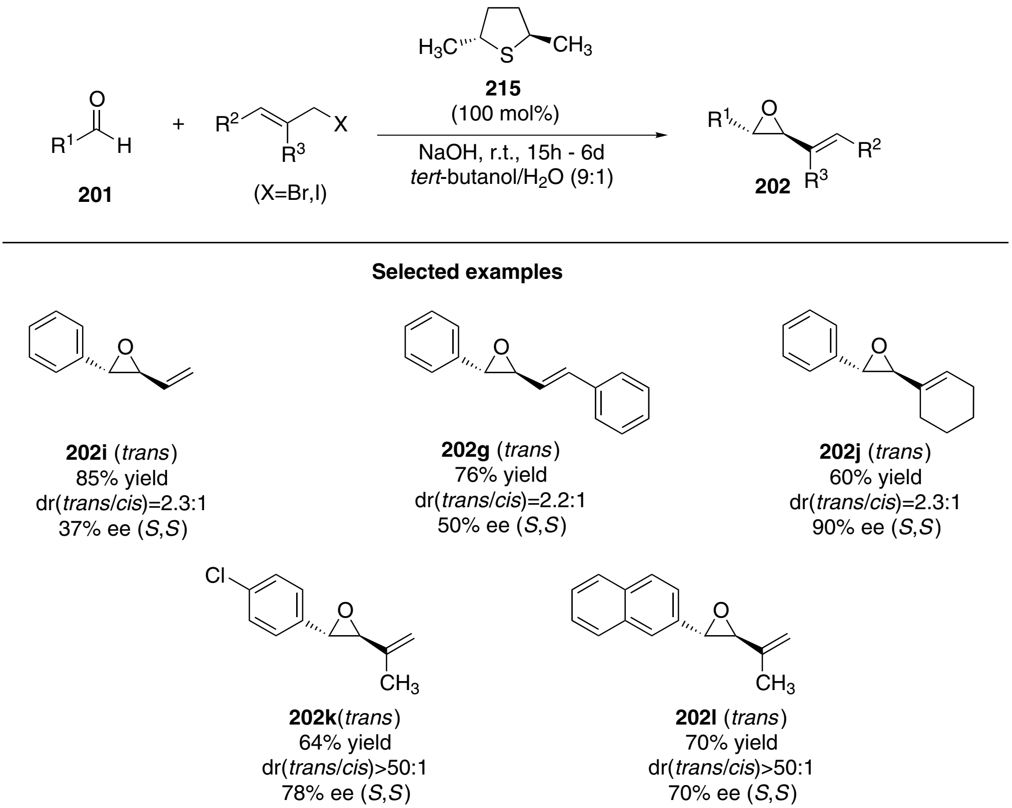
The Metzner group subsequently reported extension of this reaction by use of catalytic amounts of sulfide organocatalysts of type **215** [207]. Benzyl bromide was used as alkyl halide. It should be added that benzyl chloride was not sufficiently reactive, and that the corresponding iodide was usually not available in sufficient purity. To increase the reactivity tetra-*n*-butyl ammonium iodide was used as an additive to form *in situ* the corresponding, more reactive, iodide. Under optimized conditions numerous epoxidations were performed with catalytic amounts (10 and 20 mol%) of the chiral sulfide, e.g. **215** [207]. Selected examples are shown in Scheme 6.92. Numerous aromatic aldehydes and cinnamic aldehyde were successfully converted into the desired epoxides in high yields, although reaction times were longer (usually 4–6 days) than when stoichiometric amounts of the chiral sulfide were used. Diastereomeric ratio and enantioselectivity were usually somewhat lower than when one equivalent of the chiral sulfide organocatalyst was used. For



Scheme 6.92

example, with 10 mol% **215** as catalyst formation of (*S*,*S*)-**202b** in 77% yield required 6 days instead of 2 days for 89% yield when using one equivalent of the catalyst. The diastereomeric ratio (d.r. (trans/cis) = 90:10) and ee (72%) were in a similar range but still somewhat lower than those obtained in the presence of one equivalent of **215** (d.r. (trans/cis) = 92:8; 86% ee) [207].

The successful extension of this asymmetric reaction to the use of allyl halides (instead of benzyl halides) was also reported by the Metzner group [208]. The desired vinyl oxiranes were formed in a one-pot reaction starting from an allyl halide and an aromatic aldehyde in the presence of a sulfide, e.g. **215**, and sodium hydroxide as base. A 9:1 mixture of *tert*-butanol and water was used as solvent. The products were obtained in satisfactory to good yields (up to 85%) and enantioselectivity for the trans isomer was up to 90% ee. Diastereoselectivity was high for branched allyl halides, with d.r. (trans/cis) up to >50:1, whereas for unbranched allyl halides the diastereomeric ratio was only modest – 2.3:1 to 2.8:1. Selected examples are shown in Scheme 6.93. The methylallyl iodide or bromide was found to be the preferred allyl halide in terms of diastereoselectivity and enantioselectiv-

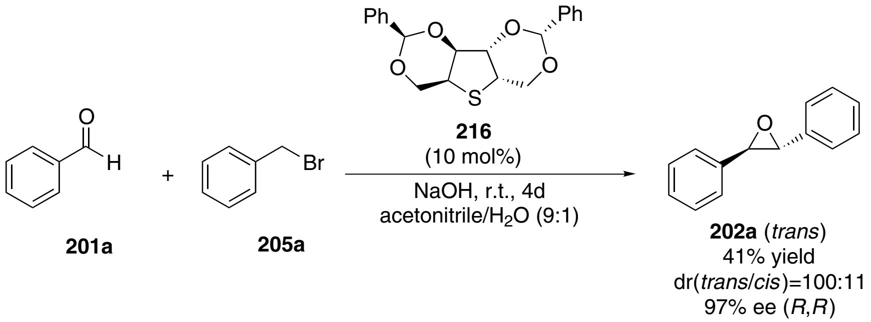


Scheme 6.93

ity. Several aromatic aldehydes other than benzaldehyde have also been used successfully, leading to comparable diastereoselectivity and enantioselectivity (Scheme 6.93). The reaction time, however, was somewhat long – usually several days. It should be added that rapid purification on silica gel was required, because of the sensitivity of the vinyl oxiranes to acid.

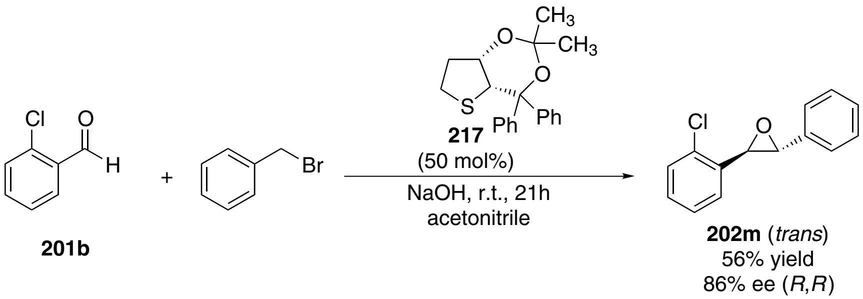
Reduction of the amount of catalyst was also investigated by the Metzner group in the epoxidation of benzaldehyde with methylallyl iodide [208]. Although use of 10 mol% **215** resulted in comparable yields, diastereomeric ratio, and enantiomeric excess, the reaction time was very long – one month. Addition of tetra-*n*-butyl ammonium iodide was not beneficial in this reaction, probably because of poor compatibility of the produced epoxide with this additive [208].

Use of a related, more bulky sulfide, the tricyclic C_2-symmetric organocatalyst **216**, has been reported by the Goodman group [209, 210]. This bulky sulfide is prepared in three steps and 76% overall yield starting from cheap and readily available D-mannitol. Use of one equivalent of this thiolane **216** in the synthesis of epoxides of type **202** resulted in a good diastereomeric ratio (d.r. (trans/cis) = 100:8) and excellent enantioselectivity (97% ee) [209]. Reactivity was, however, lower than for sulfide catalyst **215** and its ethyl-substituted analog. Thus, 7 days reaction time was needed to achieve a yield of 59% when using one equivalent of **216** as catalyst. Use of catalytic amounts (10 and 20 mol%) of **216** also led to high diastereomeric ratios and enantioselectivity of 94–98%, but reactivity decreased further. For example, in the presence of 10 mol% **216** a reaction time of 4 days was required for a yield of 41% (Scheme 6.94) [209]. Investigation of the range of substrates revealed that *p*-halogenated and *p*-nitro-substituted benzaldehydes were suitable substrates whereas no conversion was achieved when *p*-methoxybenzaldehyde was used.



Scheme 6.94

The Shimizu group investigated the potential of another structural type of sulfide organocatalyst, 5- and 6-membered cyclic sulfides [211]. These sulfides were prepared by biocatalytic reduction using baker's yeast. In particular the 5-



Scheme 6.95

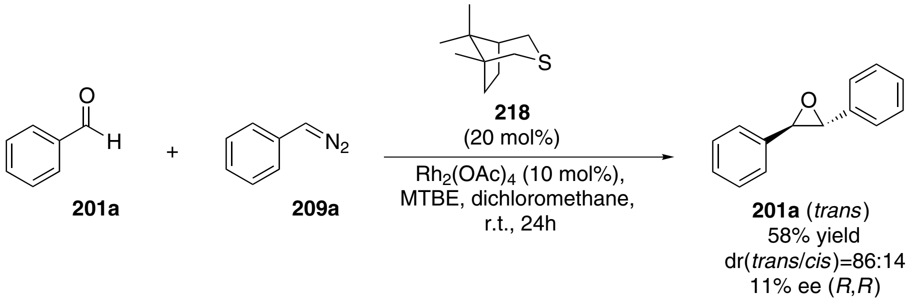
membered sulfide **217** was found to be effective in the asymmetric formation of epoxides starting from aldehydes; enantioselectivity was up to 92% ee. A representative example is shown in Scheme 6.95. In the presence of 50 mol% **217** as catalyst the trans product (*S*,*S*)-**202m** was obtained in 56% yield and with 86% ee after reaction for 21 h.

6.8.2
Epoxide Formation from Ylides Prepared by Metal-catalyzed Carbene Formation

As shown above (see also Scheme 6.87B), formation of sulfur ylides by reaction of a carbenoid with a sulfide is an efficient alternative which has also been found to be applicable to enolizable and base-sensitive aldehydes. This route, developed by the Aggarwal group, is based on use of a metal catalyst to form a carbene which subsequently reacts with the sulfide generating the sulfur ylide [200, 212, 213, 226]. Because the catalytically active species of the asymmetric process is the sulfide, this concept can be also regarded as an organocatalytic reaction.

The first step was development of a catalytic epoxidation cycle using stoichiometric amounts of achiral sulfides and rhodium acetate [212–214]. The nucleophilicity of the sulfide plays a key role. In addition, the absence of sulfides led to the formation of stilbenes, and homologated products were formed in the absence of rhodium acetate [214]. This emphasizes that the sulfide and the rhodium catalyst were required for the operation of the catalytic cycle shown in Scheme 6.87B [214]. It was also found that the reaction proceeded to completion with *catalytic* amounts of the sulfide. A prerequisite is slow addition of the diazo compound over a longer period of time, e.g. 24 h, to avoid the assumed dimerization of the diazo compound as a competing reaction under those conditions [214, 215].

The Aggarwal group also extended this concept to asymmetric epoxidation [214–216]. Initial attempts using 20 mol% sulfide **218** and 10 mol% $Rh_2(OAc)_4$ resulted in the synthesis of epoxides in satisfactory yields (58–62%) but enantioselectivity was low (11% ee). A selected example is shown in Scheme 6.96 [214]. When optically active sulfides, which are derived from camphor, are used in the presence of



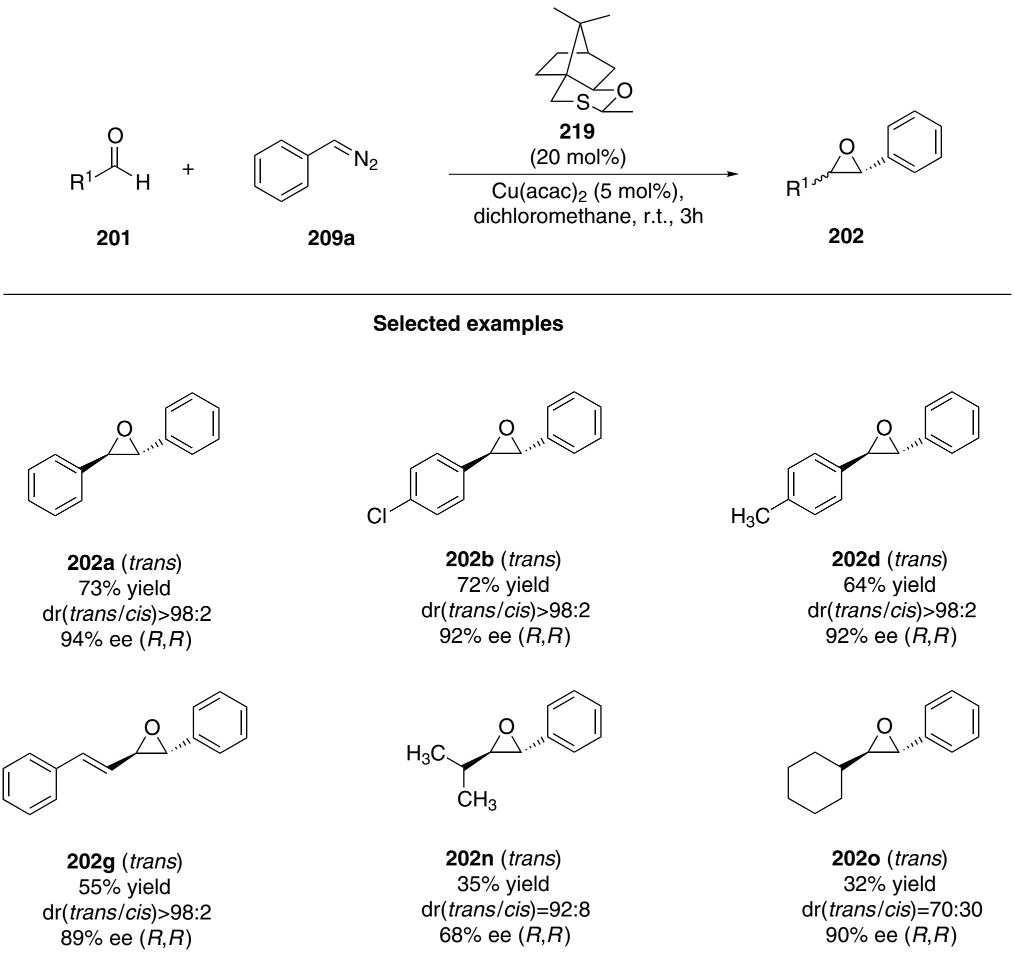
Scheme 6.96

rhodium acetate epoxides of type **202** are formed in good yields and with good diastereomeric ratio (up to d.r. (trans/cis) = 10:1). Although enantioselectivity was also improved by use of these sulfide catalysts it was still modest and did not exceed 41% ee [216].

The discovery of copper complexes as alternatives to the rhodium catalysts and optimum metal salts [215, 217, 219], and the development of an optimized sulfide, **219**, led to an improved catalytic system [218, 219]. Use of this optimized catalytic system afforded the desired products in high yield and enantioselectivity [218, 219]. Many 1,3-oxathianes based on camphorsulfonic acid were also prepared and investigated for their catalytic potential [219]. This study revealed that sulfide **219** was the preferred organocatalyst. Experiments using sulfur and carbon analogs of the 1,3-oxathiane revealed the significant effect of the oxygen of the 1,3-oxathiane in controlling the enantioselectivity of the process. This beneficial effect was explained as a result of combined anomeric and Cieplak effects. Interestingly, the optimization study showed that enantioselectivity was independent of the solvent and metal component whereas yield was influenced by both factors [219]. The optimum metal salt was copper acetylacetonate. This experimental investigation of the effect of the metal salt emphasized that the metal does not participate in the reaction of the sulfur ylide with the aldehyde component [219].

Under optimized conditions, e.g. 20 mol% **219** and pure copper(II) acetylacetonate (5 mol%), benzaldehyde was converted into the product (*R*,*R*)-*trans*-**202a** in 73% yield and with 94% ee (Scheme 6.97) [219]. The diastereoselectivity of this reaction is excellent – d.r. (trans/cis) > 98:2. The selectivity is high because of irreversible formation of the anti-betaine whereas formation of the syn-betaine is reversible [219].

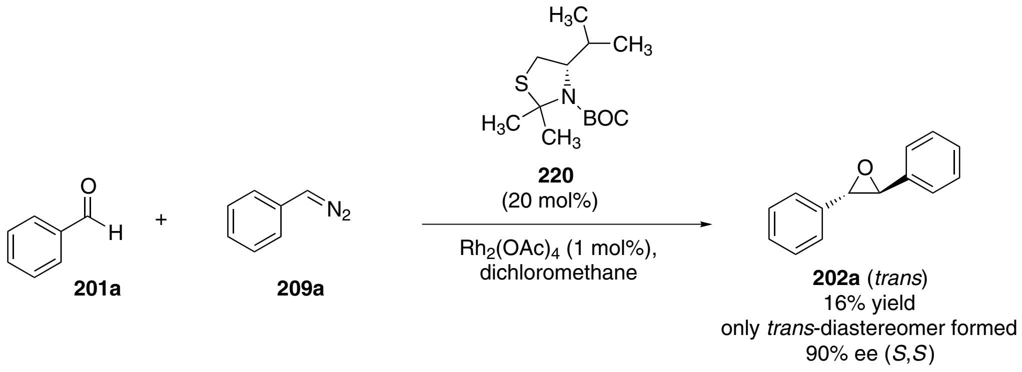
The range of substrates tolerated by this catalytic system is broad and includes other aromatic and aliphatic aldehydes (Scheme 6.97) [218, 219]. For all aromatic or α,β-unsaturated aldehydes enantioselectivity is high (89–94% ee) and diastereoselectivity is excellent (d.r. (trans/cis) > 98:2). Yields were in the range 55–73% [219]. For aliphatic aldehydes yields were significantly lower, 32–35% (Scheme 6.97) [218, 219]. Diastereoselectivity also was somewhat lower and enantioselectivity varied from 68 to 90% ee [218, 219].



Scheme 6.97

Attempts have also been made to use bifunctional catalysts in which a C_2-symmetric sulfide component is linked to the copper catalyst [220]. Although less catalyst could be used without reducing the yield (5 mol% compared with 20 mol% in the reactions already described) the enantioselectivity of these bifunctional catalysts did not exceed 24% ee.

Another type of sulfide catalyst, thiazolidine derivatives of type **220**, were designed by the Koskinen group with the aid of molecular modeling [221]. In the model reaction the thiazolidine **220** catalyzed the formation of the trans epoxide (*S*,*S*)-*trans*-**202a** highly enantioselectively (90% ee) although the yield (16%) was low (Scheme 6.98).

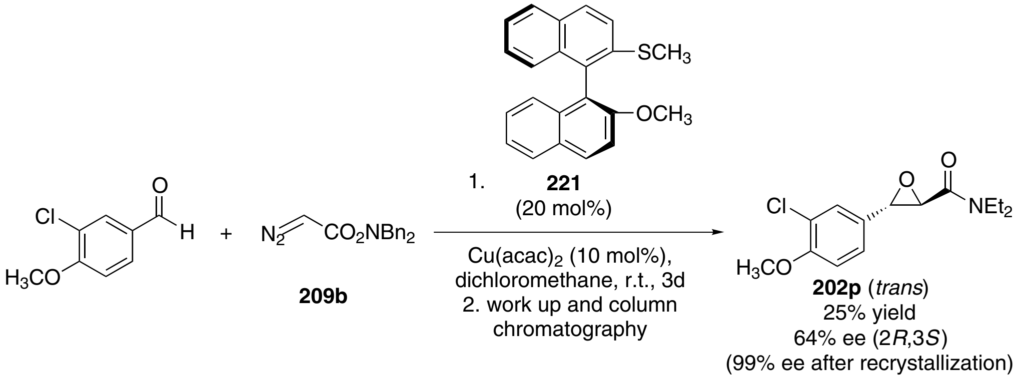


Scheme 6.98

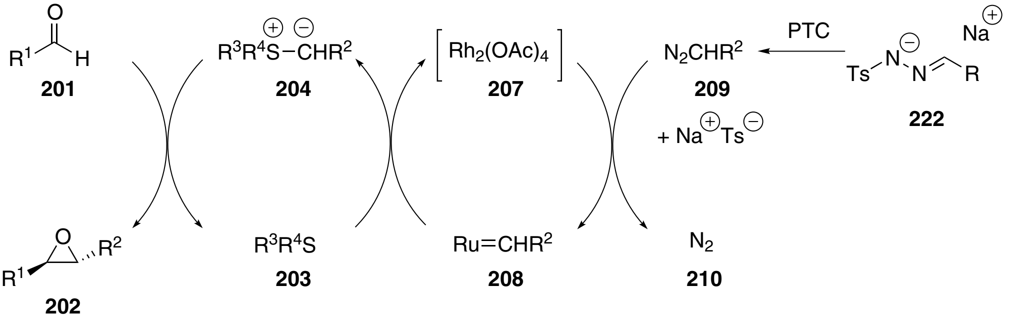
Extension of sulfur-ylide-type epoxidation to the synthesis of glycidic amides of type **202p** by use of diazoacetamide as diazo compound has been reported by Seki and co-workers [222]. The products are interesting intermediates in the preparation of pharmaceutically important products. For example, these types of epoxide are useful for synthesis of β-amino-α-hydroxy carboxylic acids, or for synthesis of diltiazem. The sulfur ylides were generated *in situ* from diazoacetamides (e.g. **209b**) in the presence of catalytic amounts of optically active binaphthylsulfide (20 mol%) and a copper(II) complex (10 mol%). The most efficient combination was **221** as binaphthylsulfide component and the *N*,*N*-dibenzyl-substituted amide **209b** as diazoacetamide component. The resulting yields and enantioselectivity, were however, moderate – 25 to 71% and 39 to 64% ee, respectively. It was found that electron-deficient aldehydes gave better yields. Interestingly, enantioselectivity can be greatly enhanced by a single recrystallization, as was demonstrated in the synthesis of **202p** (25% yield, 64% ee), for which enantioselectivity was increased to 99% ee by one recrystallization. This synthesis of **202p**, as a selected example, is shown in Scheme 6.99 [222].

Despite efficient conversions, a major drawback from practical and safety considerations is the use of (potentially) explosive diazo compounds. Consequently, the application was limited to small (mmol)-scale. Thus, replacement of the direct use of the diazo compound by suitable precursors which form the desired diazo compound *in situ* would be much more favorable. A remarkable improvement addressing this issue was recently achieved by the Aggarwal group [223, 224]. The key step was *in-situ* formation of the diazo compound starting from the tosylhydrazone salt **222** under conditions (phase-transfer catalysis at 40 °C) compatible with the sulfur-ylide type epoxidation [223]. The concept of this improved method is shown in Scheme 6.100.

Sulfide **219**, which has been shown to be an efficient organocatalyst when using phenyldiazomethane directly (Scheme 6.97), was, however, unstable under these new reaction conditions and gave the products in low yield (although enantio-

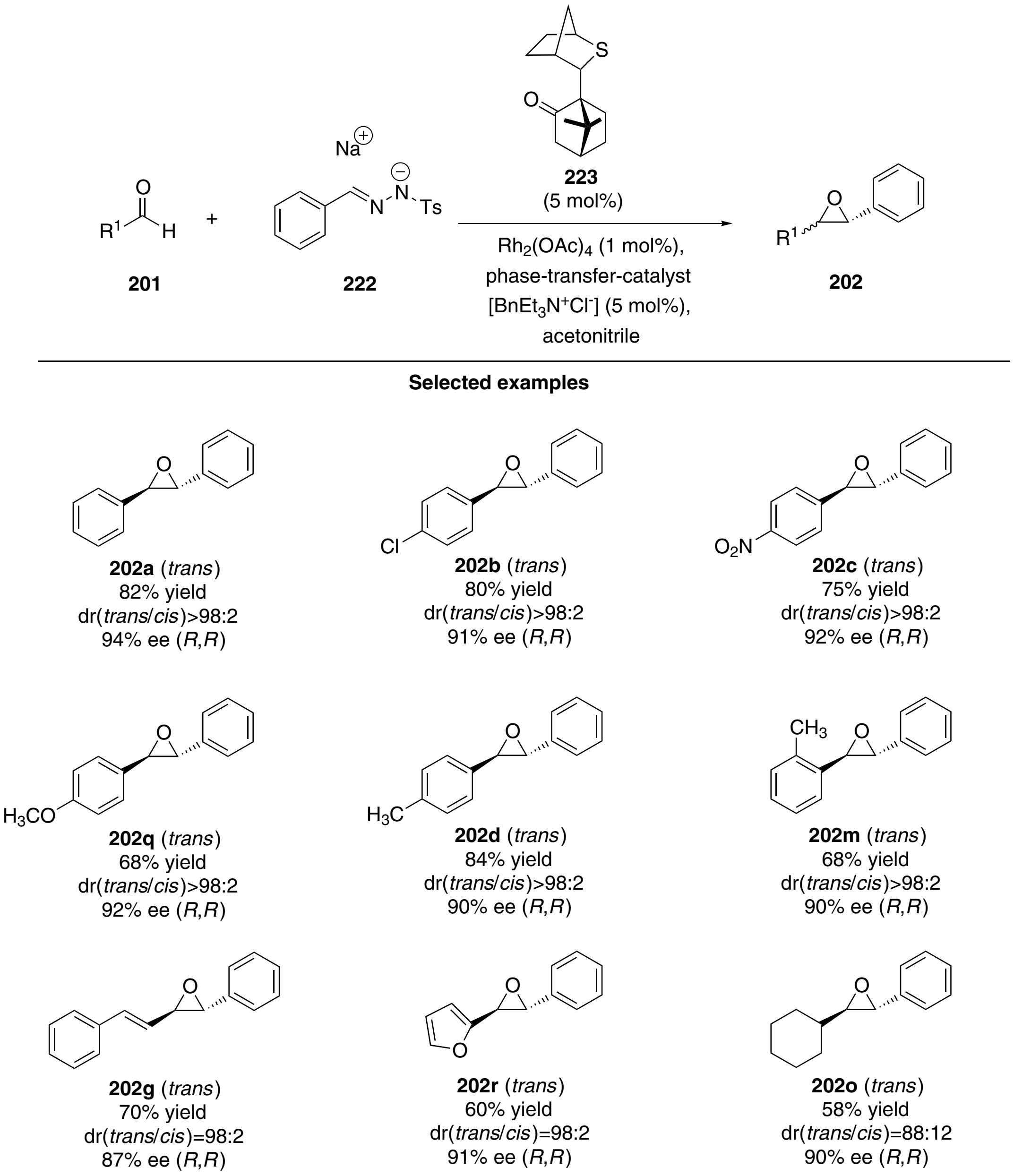


Scheme 6.99

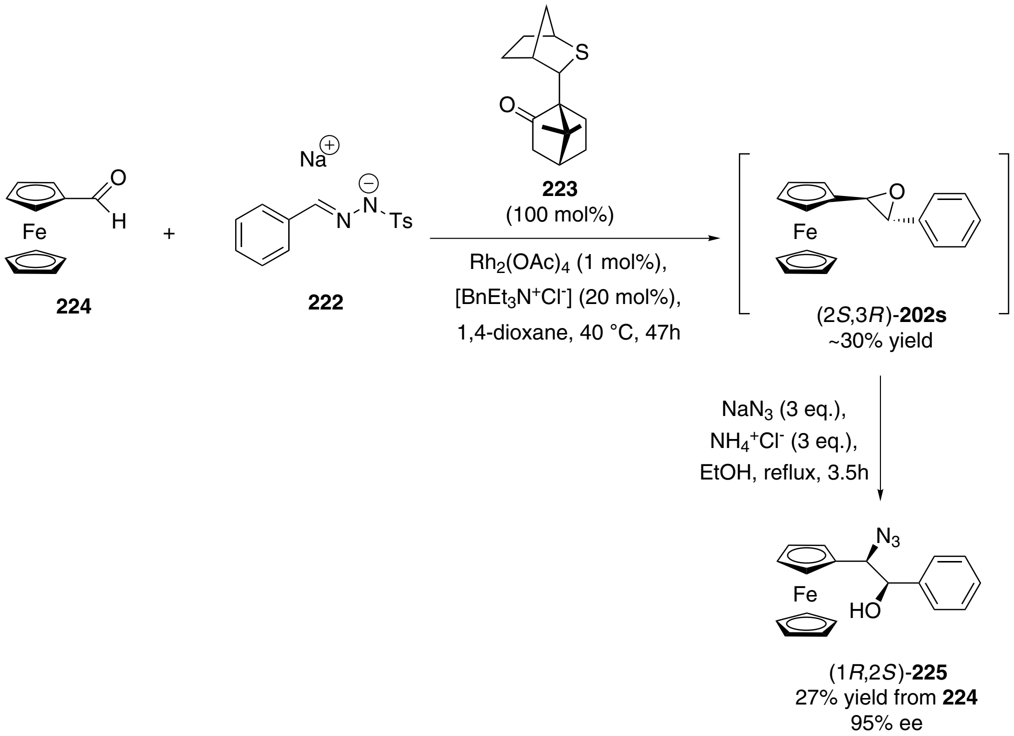


Scheme 6.100

selectivity was high). Broad catalyst screening was therefore conducted by the Aggarwal group for this type of one-pot multi-step reaction [224]. This study comprised investigation of sulfides derived from camphor, novel chiral thianes and 1,4-oxathianes, and several C_2-symmetric chiral sulfides. None of these sulfides led to both high yield and high enantioselectivity, however. In particular, the enantioselectivity varied substantially and was often moderate only. On the basis of the conclusion that this unsatisfactory enantioselectivity was a result of poor control of the conformation of the ylide, the Aggarwal group designed a new class of sulfide which were conformationally much more rigid [223, 224]. Sulfide **223**, in particular, was found to be very efficient, leading to high yields and high enantioselectivity [223, 224]. Starting from numerous aromatic aldehydes and only 5 mol% **223** as catalyst the desired epoxides were formed in good yields with excellent diastereomeric ratio of d.r. (trans/cis) $\geq$ 98:2, and high enantioselectivity in the range 90–94% ee [223]. Selected examples are shown in Scheme 6.100. *trans*-Cinnamic aldehyde and cyclohexane carboxaldehyde are also suitable substrates, leading to the epoxides **202g**, and **202o**, respectively, with high enantioselectivity (Scheme 6.101). In the latter reaction, however, the diastereoselectivity was somewhat lower. A first


Na⊕
⊖
N
N
Ts
O
R1
H
+
201
222
S
O
223
(5 mol%)
Rh2(OAc)4 (1 mol%),
phase-transfer-catalyst
[BnEt3N+Cl-] (5 mol%),
acetonitrile
O
R1
202
Selected examples
O
202a (trans)
82% yield
dr(trans/cis)>98:2
94% ee (R,R)
O
Cl
202b (trans)
80% yield
dr(trans/cis)>98:2
91% ee (R,R)
O
O2N
202c (trans)
75% yield
dr(trans/cis)>98:2
92% ee (R,R)
O
H3CO
202q (trans)
68% yield
dr(trans/cis)>98:2
92% ee (R,R)
O
H3C
202d (trans)
84% yield
dr(trans/cis)>98:2
90% ee (R,R)
CH3
O
202m (trans)
68% yield
dr(trans/cis)>98:2
90% ee (R,R)
O
202g (trans)
70% yield
dr(trans/cis)=98:2
87% ee (R,R)
O
O
202r (trans)
60% yield
dr(trans/cis)=98:2
91% ee (R,R)
O
202o (trans)
58% yield
dr(trans/cis)=88:12
90% ee (R,R)

Scheme 6.101

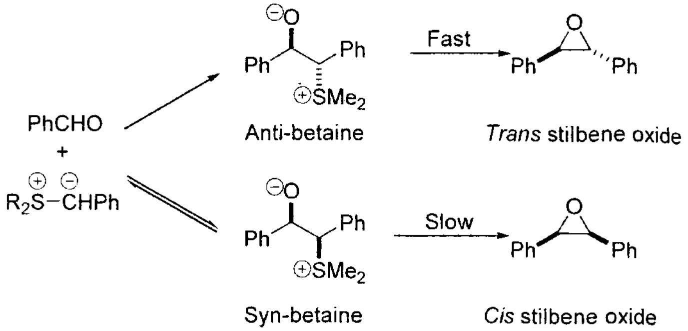


Scheme 6.102

scale up was also performed in which epoxide **202a** was prepared in a 50 mmol-scale reaction. It should be added that in addition to being a safer, highly efficient epoxidation process the overall economy of this one-pot reaction is also substantially improved.

This new method based on tosylhydrazones has also been applied by the Aggarwal group to the first synthesis of epoxyferrocene, **202s** [225]. Starting from ferrocenecarbaldehyde, **224**, and benzaldehyde tosylhydrazone sodium salt **222** the desired product **202s** was formed with high enantioselectivity, although yield was approximately 30% only (Scheme 6.102). Enantiomeric excess (95% ee) was determined for derivative **225**, obtained after subsequent epoxide opening reaction with sodium azide. One equivalent of the sulfide **223** was used for the epoxidation reaction.

The process development for this efficient Aggarwal-type sulfur-ylide epoxidation has recently been summarized in review [226]. Several detailed studies of the reaction mechanism have also recently been reported [227–230]. In particular, a comprehensive experimental and computational investigation of the reaction mechanism has been performed by the Aggarwal group [227, 228]. The two diastereoselective pathways for synthesis of *trans*- and *cis*-stilbene oxides, as representative examples, are shown in Scheme 6.103 [228]. The initial step is addition of the sulfur ylide to the C=O double bond of the aldehyde with formation of the cor-



Scheme 6.103 (from Ref. [228] with permission of the ACS)

responding anti and syn betaine intermediates, respectively. Subsequently, elimination of the sulfide from these betaines gives the desired trans or cis epoxide [227, 228]. The high trans diastereoselectivity was found to result from fast and irreversible ring closure of the formed anti betaine. In contrast, elimination of the sulfide from the syn betaine under formation of the cis-product is slow, and competitive reversion to the reactants occurs. Consequently, high trans diastereoselectivity is observed for the sulfur-ylide-type epoxidation.

The structures of the corresponding transition states have been investigated by Aggarwal and co-workers for the model reaction of benzaldehyde and dimethylsulfonium benzylide [228]. The different approaches in this reaction of the sulfur ylide with the aldehyde and the corresponding stereochemical outcomes are shown in Figure 6.1. Interestingly, the computational study revealed that the mechanism involves cisoid transition states for formation of the betaine. The energy barriers leading to the cisoid rotamers are lower than for the transoid analogs. Thus, the transition states leading to transoid betaine formation are not expected to play any role in the mechanism. The initial C–C bond-formation leading to the two diastereomeric cisoid betaines proceeds at a similar rate. In the anti pathway, which gives the trans epoxide, this initial addition was found to be rate-determining whereas subsequent C–C bond rotation and elimination occur easily. In contrast, for the syn pathway, leading to the cis epoxide, C–C bond rotation is slow. Thus, this torsional rotation is the rate-determining step. Consequently, reversion to reactants occurs for this pathway and so cis products are formed as the minor product and the trans epoxides are the major diastereomers. These computational results explaining the high trans diastereoselectivity are in excellent agreement with the experiment.

Conclusion

Asymmetric sulfur-ylide-type epoxidation is an excellent tool for enantioselective and diastereoselective synthesis of epoxides. By use of Aggarwal-type methodology a broad range of aromatic, enolizable, and base-sensitive aldehydes can be converted into the desired epoxides. In addition to an excellent diastereomeric ratio, the optimized organocatalytic systems of this sulfur-ylide-type epoxidation also

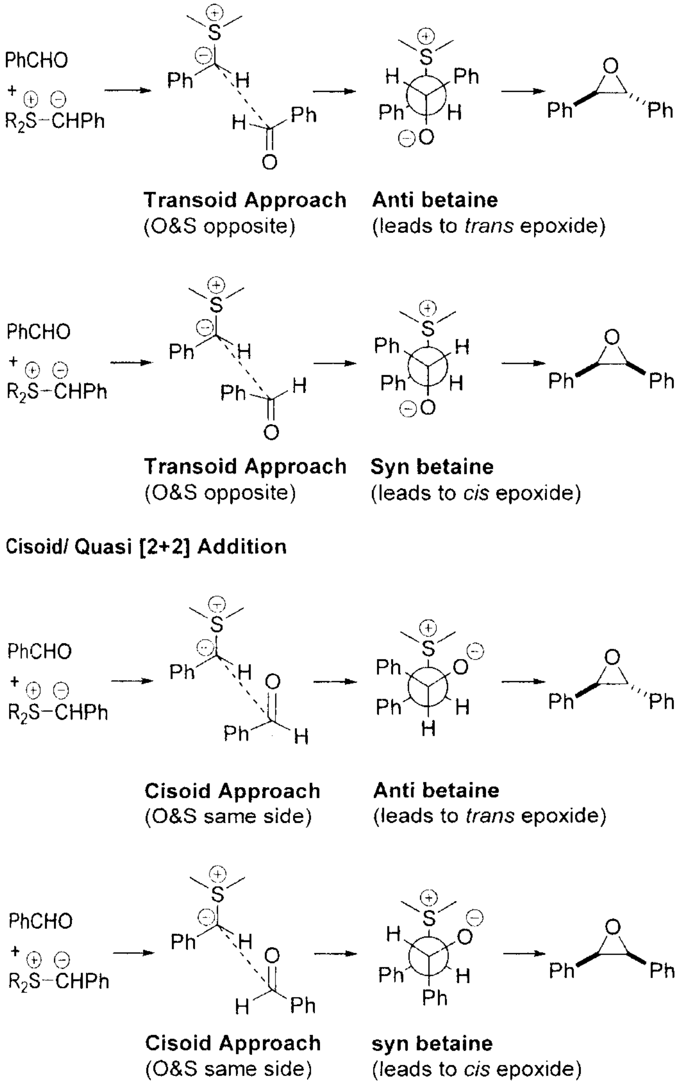
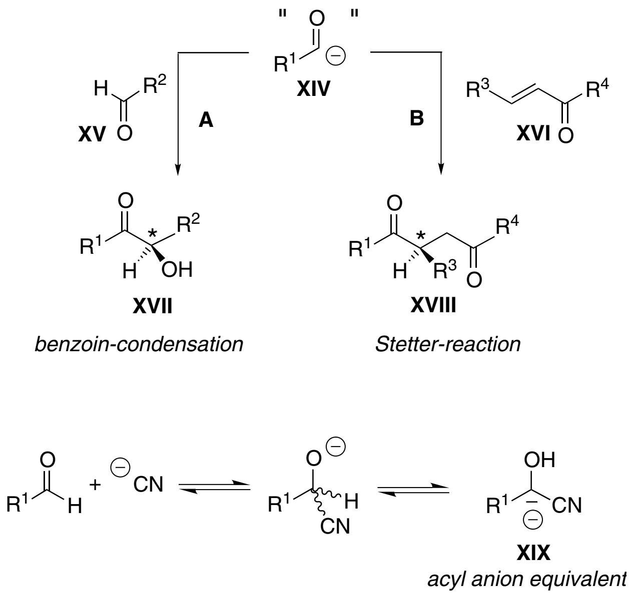


Fig. 6.1 (from Ref. [228] with permission of the ACS)

lead to high enantioselectivity. The range of application of this sulfur-ylide-type epoxidation has already been shown to be broad.

6.9 The Benzoin Condensation and the Stetter Reaction

The general reaction patterns of the benzoin condensation and the related Stetter reaction are depicted in Scheme 6.104. Both reactions are nucleophilic acylations,

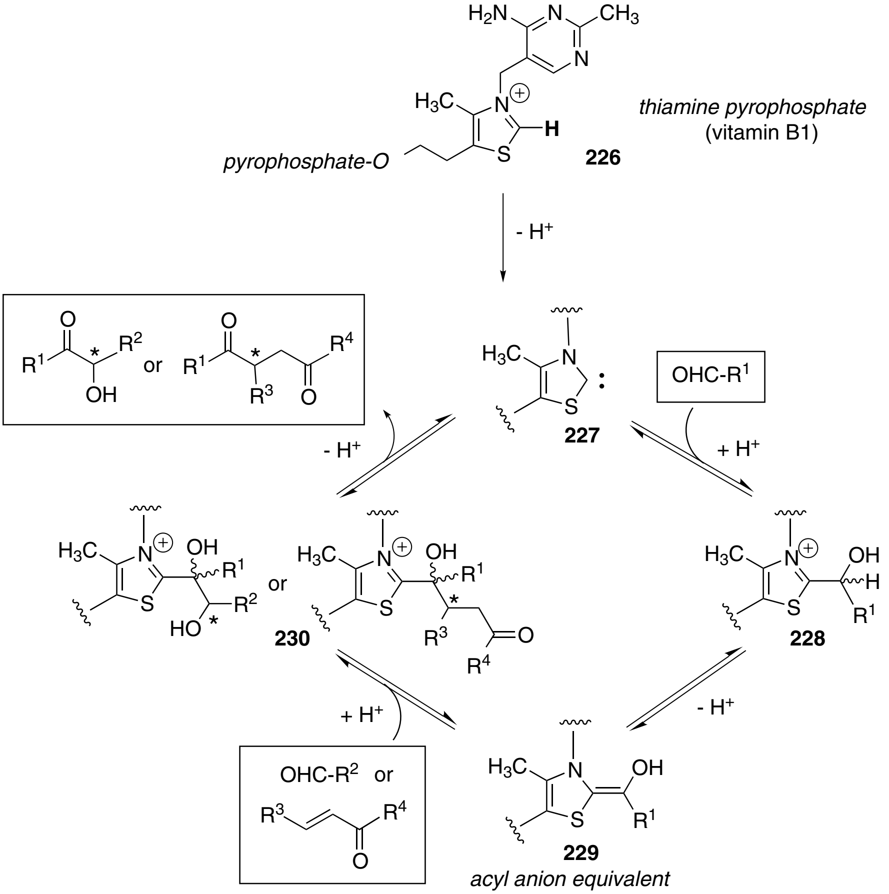


Scheme 6.104

i.e. addition of an acyl anion equivalent, **XIV**, to an electrophilic acceptor. In the benzoin condensation (Scheme 6.104, path A) a 2-hydroxyketone **XVII** results from addition to an aldehyde **XV** whereas the Stetter reaction (Scheme 6.104, path B) provides 2-substituted 1,4-dicarbonyl compounds, **XVIII**, by addition of the acyl anion equivalent **XIV** to enones and enoates **XVI**. Other Michael-acceptors can also be used [231, 232]. Both reactions are of great synthetic utility [231].

In both reactions cyanide has usually been employed as catalyst [231, 232]. Under these conditions, the acyl anion equivalent is represented by the tautomeric form **XIX** of the cyanohydrin anion which results from addition of cyanide to an aldehyde (Scheme 6.104). In nature, this type of Umpolung is performed enzymatically, with the aid of the cofactor thiamine pyrophosphate **226** (vitamin B1, Scheme 6.105) [232, 233].

In the thiazolium cation the proton in the 2-position is acidic and its removal gives rise to the ylide/carbene **227**. This nucleophilic carbene **227** can add, e.g., to an aldehyde to produce the cationic primary addition product **228**. The latter, again via C-deprotonation, affords the enamine-like structure **229**. Nucleophilic addition of **229** to either an aldehyde or a Michael-acceptor affords compound(s) **230**. The catalytic cycle is completed by deprotonation and elimination of the carbene **227**. Strictly speaking, the thiazolium salts (and the 1,2,4-triazolium salts discussed below) are thus not the actual catalysts but *pre-catalysts* that provide the catalytically active nucleophilic carbenes under the reaction conditions used. This mechanism of action of thiamine was first formulated by Breslow [234] and applies to the benzoin and Stetter-reactions catalyzed by thiazolium salts [235–237] and to those

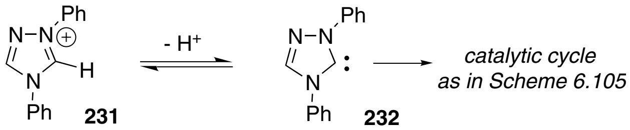


Scheme 6.105

effected by other nucleophilic carbenes, for example the 1,2,4-triazolylidenes (*vide infra*). In this context, the intermediate **229** is often referred to as the Breslow intermediate.

6.9.1
The Benzoin Condensation

Early approaches toward catalytic asymmetric benzoin condensation by Sheehan et al. [238, 239], Tagaki et al. [240], and Zhao et al. [241] concentrated on chiral thiazolium systems. The same is true for more recent investigations by Leeper [242], Rawal [243], and López-Calahorra et al., the last of whom used bridged bis-thiazolium salts [244]. In these studies the feasibility in principle of asymmetrically catalyzed benzoin condensation was proven and enantiomeric excesses up to

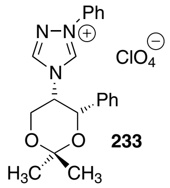


Scheme 6.106

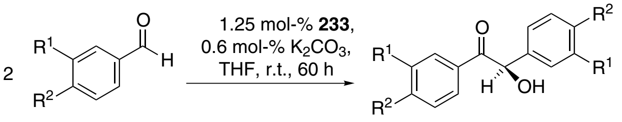
57% were reported [241, 245]. A breakthrough in the field was achieved in 1996 when Teles et al. showed that readily available 1,2,4-triazolium salts such as **231** are highly efficient catalysts of the condensation of formaldehyde to give glycolaldehyde (Scheme 6.106) [246]. These materials proved to be catalytically much more active than the original thiazolium salts. Mechanistic investigations indicated that catalysis is effected by the nucleophilic carbenes, for example **232**, formed on deprotonation (Scheme 6.106). In other words, the Breslow-mechanism shown in Scheme 6.105 for thiazolium salts also applies to the 1,2,4-triazolium systems [246]. It should, however, be pointed out that – where applicable – product composition can be significantly different. For example, whereas thiazolium catalysts afford exclusively dihydroxyacetone with formaldehyde as substrate, the triazolium systems afford glycolic aldehyde (plus glyceraldehyde and C_4 and C_5 sugars as secondary products) [246]. Catalyst-dependent differences in the relative rates of the partial reactions within the catalytic cycle (Scheme 6.105) most probably account for this phenomenon. A subsequent study by Enders et al. on chiral triazolium salts identified the derivative **233** as a first catalyst for the asymmetric benzoin condensation that affords substantial enantiomeric excesses (up to 86%) with satisfactory chemical yields (Table 6.3) [247].

Most remarkably, catalyst loadings could be reduced to 1.25 mol%, resulting in total turnover numbers > 50 (Table 6.3) [247]. Catalyst **233** is readily available in large quantities because its synthesis is based on (*S*,*S*)-(+)-5-amino-2,2-dimethyl-4-phenyl-1,3-dioxane, an intermediate of industrial chloramphenicol production [247]. The more rigid bicyclic triazolium systems **234**, **235**, and **236** were synthesized by Leeper and Knight from phenylalanine and pyroglutamic acid (Table 6.4) [248]. The related and even more enantioselective catalyst **237** was reported by Enders and Kallfass in 2002 [249]. The bicyclic triazolium salt **237** is derived from L-*tert*-leucine (five steps) [249]. The results obtained with catalysts **234**–**237** in asymmetric benzoin condensations are summarized in Table 6.4. Although the enantioselectivity achieved with the bicyclic compounds **234**–**236** is comparable with that observed with the triazolium system **233** (Table 6.3), it should be noted that significantly higher catalyst loadings are required for **234**–**236** (5–30 mol%) than for **233** (1.25 mol%). The highest enantioselectivity yet achieved was with the bicyclic triazolium salt **237** by Enders and Kallfass [249]. Inspection of Table 6.4 also reveals that benzaldehyde and electron-rich derivatives thereof afford the best enantioselectivity (up to 95% ee) whereas the asymmetric induction achieved with electron-deficient aldehydes is substantially lower. Finally, when the amount of catalyst **237** was reduced to 2.5 mol%, benzaldehyde could be converted to benzoin with 99% ee, albeit with reduced chemical yield (33%) [249]. The latter behavior is typical of

Tab. 6.3



233



R¹	*R¹*	*Yield [%]*	*ee [%]*
H	H	66	75
H_3CO	H	41	66
H	H_3CO	22	86
CH_3	H	65	76
H	CH_3	46	82
H	F	48	44
H	Cl	51	29
H	Br	72	20

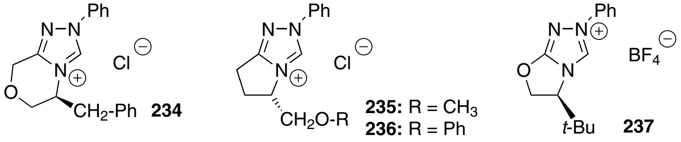
benzoin condensations and reflects the sensitivity of the reaction product toward base-induced racemization. Clearly, the catalytically active nucleophilic carbenes are also bases. To obtain good enantioselectivity and chemical yields it is, therefore, necessary to carefully balance and optimize the base and catalyst loadings, reaction conditions, etc. In fact, the lower basicity of the triazolylidenes compared with the thiazolylidenes [246] can be considered as a key feature responsible for the much better ee achieved with the former catalysts than with the latter.

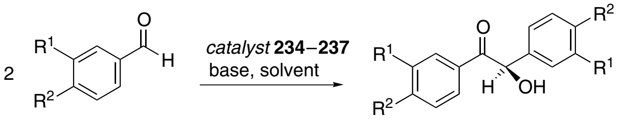
The thiazolium and, particularly, triazolium catalysts discussed above have been developed to the extent that they perform remarkably well in the asymmetric benzoin condensation of aromatic aldehydes. Triazolium catalysts are also very effective in the (non-stereoselective) condensation of aliphatic aldehydes [250]. It seems, however, that no catalyst is yet available that enables condensation of aliphatic aldehydes with synthetically useful enantioselectivity. The best ee yet obtained are in the range 20–25%, e.g. in the dimerization of the straight-chain C_2–C_7 aldehydes [251].

6.9.2
The Stetter Reaction

The triazolium catalysts discussed above do not efficiently promote the Stetter reaction, i.e. the formation of 1,4-dicarbonyl compounds from aldehydes and α,β-

Tab. 6.4



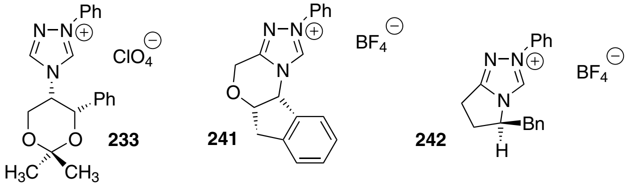


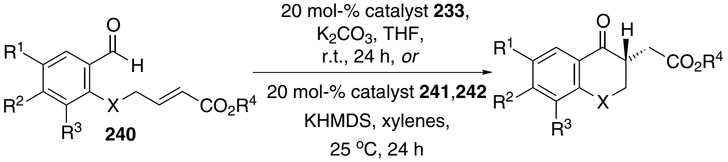
bases: **234–236**: 5-30 mol-% Et_3N; **237**: 10 mol-% KO*t*-Bu
solvent: **234–236**: MeOH; **237**: THF
reaction times: **234–236**: 18-48 h; **237**: 16 h

R^1	R^1	Catalyst (mol-%)	Temp. [°C]	Yield [%]	ee [%]	Ref.
H	H	**234** (30)	r.t.	45	80	248
H	H	**235** (30)	r.t.	47	48	248
H	H	**236** (30)	r.t.	22	63	248
H	H	**237** (10)	18	83	90	249
H	H_3CO	**237** (10)	18	8	95	249
CH_3	H	**237** (10)	0	36	91	249
H	CH_3	**234** (30)	r.t.	38	82.5	248
H	CH_3	**235** (30)	r.t.	28	61	248
H	CH_3	**236** (30)	r.t.	11	69	248
H	CH_3	**237** (10)	18	16	93	249
H	F	**237** (10)	18	81	83	249
H	F	**237** (10)	0	61	91	249
Cl	H	**237** (10)	0	85	86	249
H	Cl	**234** (10)	r.t.	11	76	248
H	Cl	**235** (30)	r.t.	27	40	248
H	Cl	**236** (5)	r.t.	12	65	248
H	Cl	**237** (10)	0	44	89	249
H	Br	**237** (10)	0	59	91	249

enones, enoates, etc. (Scheme 6.104B). This might be because the nucleophilic triazolylidene carbene catalysts derived from the pre-catalysts form *stable* adducts with α,β-enones, etc. [252, 253]. In the *intramolecular* Stetter reaction of the highly reactive *ortho*-crotyloxybenzaldehydes **240**, however, quite substantial enantioselectivity (up to 74% ee) was achieved for the first time in 1996 by Enders et al., who used the triazolium catalyst **233** (Table 6.5; see Table 6.3 for application of the catalyst **233** in the benzoin condensation) [254]. More recent work by Rovis et al. identified the aminoindanol- and phenylalanine-derived triazolium systems **241** and **242**, respectively, as the most enantioselective catalysts for the intramolecular Stetter reac-

Tab. 6.5

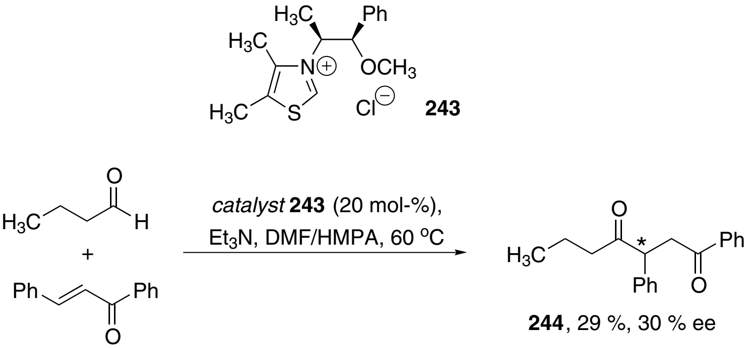




R^1	R^2	R^3	R^4	X	Catalyst	Yield [%]	ee [%]	Ref.
H	H	H	Me	O	**233**	73	60	254
H	H	H	Et	O	**233**	69	56	254
H	H	H	Et	O	**241**	94	94	255
Me	H	H	Et	O	**241**	80	97	255
H	H	Me	Et	O	**241**	90	84	255
H	H	H_3CO	Me	O	**233**	44	68	254
H	H	H_3CO	Et	O	**233**	69	62	254
H	H	H_3CO	Et	O	**241**	95	87	255
H	H_3CO	H	Me	O	**233**	22	74	254
H_3CO	H	H	Me	O	**233**	56	61	254
Cl	H	H	Me	O	**233**	50	41	254
H	H	H	Et	S	**241**	63	96	255
H	H	H	Et	NMe	**241**	64	82	255
H	H	H	Et	CH_2	**241**	35	94	255
H	H	H	Et	CH_2	**242**	90	92	255

tion of substrates **240** (Table 6.5) [255]. With these catalysts enantiomeric excesses up to 97% and quite satisfactory yields were achieved. Rovis and Kerr also studied the effect on the efficiency of their catalytic asymmetric Stetter reaction of the type of electron-withdrawing group in the Michael acceptor. Whereas the ester, ketone, and nitrile of general structure **240** performed well, the amide, aldehyde, and nitro-olefin did not cyclize under the conditions given in Table 6.5 [256]. Similarly, for purely aliphatic aldehyde substructures an alkylidene malonate acceptor proved superior to an enone.

There seems to be one example only of a catalytic intermolecular asymmetric Stetter reaction. As shown in Scheme 6.107, Enders reported that the thiazolium cation **243** afforded a moderate enantiomeric excess in the coupling of *n*-butanal with *E*-chalcone to give the 1,4-diketone **244** [257].



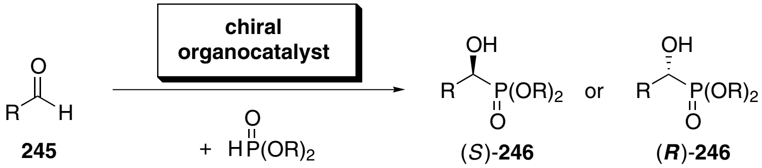
Scheme 6.107

Conclusions

"Azolium"-catalyzed formation of 2-hydroxycarbonyl and 2-substituted 1,4-dicarbonyl compounds are prime examples of bio-inspired processes using low-molecular weight catalysts. Whereas the natural cofactor thiamine and early man-made catalysts incorporated the thiazolium heterocycle, the most synthetically useful organocatalysts currently available are based on chiral derivatives of the 1,2,4-triazolium system. With the aid of these organocatalysts developed mainly by Enders, Teles et al., very good yields and enantiomeric excesses (up to 99%) have been achieved in the benzoin condensation of aromatic aldehydes, particularly if electron-rich. Similarly, the intramolecular Stetter-cyclization of 2-crotyloxy-benzaldehydes has been achieved with enantiomeric excesses up to 97%. Unfortunately, the triazolium catalysts perform less effectively in the intermolecular Stetter reaction of enones, which is thus restricted to the less active and selective thiazolium catalysts (ee up to 30%). It is hoped that further improvement of these most interesting classes of organocatalyst might eventually enable highly enantioselective dimerization of aliphatic aldehydes also.

6.10
Hydrophosphonylation of C=O Double Bonds

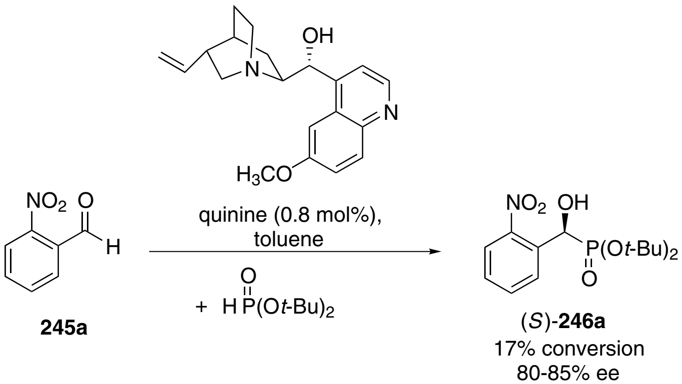
Asymmetric catalytic addition of dialkylphosphites to a C=O double bond is a powerful method, and probably the most general and widely applied, for formation of optically active α-hydroxy phosphonates [258]. The basic principle of this reaction is shown in Scheme 6.108. Several types of catalyst have been found to be useful. The transition-metal-catalyzed asymmetric hydrophosphonylation using chiral titanium or lanthanoid complexes was developed by several groups [259, 260]. The most efficient type of chiral catalyst so far is a heterobimetallic complex consisting



Scheme 6.108

of a lanthanoid metal center with chiral (substituted) binaphthol ligands [260]. In the presence of this type of catalyst, developed by Shibasaki and co-workers, the desired products were obtained in yields of up to 95% and with high enantioselectivity (up to 95% ee) [260].

In addition to metals it has been found that organic cinchona alkaloids are also useful catalysts [261, 262]. Interestingly, the organocatalytic asymmetric formation of α-hydroxy phosphonates – developed by Wynberg et al. in 1983 – was the first ever example of an asymmetric catalytic hydrophosphonylation of an aldehyde [261, 262]. The cinchona alkaloid quinine, an inexpensive and readily available compound was used as organocatalyst. In the presence of a very small amount of catalyst, only 0.8 mol%, quinine catalyzed the addition of dimethyl phosphite to *o*-nitrobenzaldehyde in dry toluene within 12 h [261]. Although the conversion was quantitative, enantioselectivity, 28% ee, was unsatisfactory. In the presence of quinidine as organocatalyst the same optical rotation was obtained whereas use of *O*-acetylquinidine as catalyst furnished a racemate. Use of sterically more demanding alkyl ester moieties resulted in substantially increased enantioselectivity. Although use of di-*tert*-butyl phosphite as a phosphite component (Scheme 6.109) gave the desired α-hydroxy phosphonates with high enantioselectivity (80–85% ee), the rate of reaction decreased when increasing bulkiness of the ester group. For di-*tert*-butyl phosphite conversion was only 17%.



Scheme 6.109

Use of *o*-nitrobenzaldehyde as the aldehyde was particularly successful [261] and use of other aromatic aldehydes as substrates, e.g. *o*-chlorobenzaldehyde, also worked well [262].

The dialkyl phosphites can be readily converted into their corresponding "free" α-hydroxy phosphonic acids, as has been shown by Wynberg and co-workers [261].

References

1 For recent reviews/highlights on the asymmetric synthesis (by enzymatic, organocatalytic and organometallic methods) of cyanohydrins and their applications, see references 2–8.

2 (a) M. North, *Tetrahedron: Asymmetry* **2003**, *14*, 147–176; (b) M. North, *Synlett* **1993**, 807–820.

3 L. Yet, *Angew. Chem.* **2001**, *113*, 900–902; *Angew. Chem. Int. Ed. Engl.* **2001**, *40*, 875–877.

4 D. Enders, J. P. Shilvock, *Chem. Soc. Rev.* **2000**, *29*, 359–373.

5 R. J. H. Gregory, *Chem. Rev.* **1999**, *99*, 3649–3682.

6 M. Arend, *Angew. Chem.* **1999**, *111*, 3047–3049; *Angew. Chem. Int. Ed.* **1999**, *38*, 2873–2874.

7 F. Effenberger, *Angew. Chem.* **1994**, *106*, 1609–1619; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1555–1563.

8 J.-M. Brumel, I. P. Holmes, *Angew. Chem.* **2004**, *116*, 2810–2837; *Angew. Chem. Int. Ed.* **2004**, *43*, 2752–2778.

9 G. Bredig, W. S. Fiske, *Biochem. Z.* **1912**, 7.

10 G. Bredig, M. Minaeff, *Biochem. Z.* **1932**, *249*, 241–244.

11 V. Prelog, M. Wilhelm, *Helv. Chim. Acta* **1954**, *37*, 1634–1661.

12 H. Albers, E. Albers, *Z. Naturforsch.* **1954**, *9b*, 133–145.

13 H.-H. Hustedt, E. Pfeil, *Liebigs Ann. Chem.* **1961**, *640*, 15–28.

14 See refs. 15, 16 for further early work using poly(L-iminoisobutylethylene) [15] and linear or cyclic dipeptides derived from histidine and alanine [16], affording enantiomeric excesses < 20%.

15 S. Tsuboyama, *Bull. Chem. Soc. Jpn.* **1962**, *35*, 1004.

16 J.-I. Oku, N. Ito, S. Inoue, *Makromol. Chem.* **1979**, *180*, 1089–1091.

17 H. Gountzos, W. R. Jackson, K. J. Harrington, *Aust. J. Chem.* **1986**, *39*, 1135–1140.

18 (a) J.-I. Oku, S. Inoue, *J. Chem. Soc., Chem. Commun.* **1981**, 229–230; (b) J.-I. Oku, N. Ito, S. Inoue, *Macromol. Chem.* **1982**, *183*, 579–589.

19 S. Asada, Y. Kobayashi, S. Inoue, *Makromol. Chem.* **1985**, *186*, 1755–1762.

20 Y. Kobayashi, S. Asada, I. Watanabe, H. Hayashi, Y. Motoo, S. Inoue, *Bull. Soc. Chem. Jpn.* **1986**, *59*, 893–895.

21 Y. Kobayashi, H. Hayashi, K. Miyaji, S. Inoue, *Chem. Lett.* **1986**, 931–934.

22 B. R. Matthews, W. R. Jackson, G. S. Jayatilake, C. Wilshire, H. A. Jacobs, *Aust. J. Chem.* **1988**, *41*, 1697–1709.

23 K. Tanaka, A. Mori, S. Inoue, *J. Org. Chem.* **1990**, *55*, 181–185.

24 H. J. Kim, W. R. Jackson, *Tetrahedron: Asymmetry* **1994**, *5*, 1541–1548.

25 C. R. Noe, A. Weigand, S. Pirker, *Monatsh. Chem.* **1996**, *127*, 1081–1097.

26 W. R. Jackson, G. S. Jayatilake, B. R. Matthews, C. Wilshire, *Aust. J. Chem.* **1988**, *41*, 203–213.

27 C. R. Noe, A. Weigand, S. Pirker, P. Liepert, *Monatsh. Chem.* **1997**, *128*, 301–316.

28 J. C. Thoen, M. A. Lipton, *Tetrahedron: Asymmetry* **1997**, *8*, 3947–3954.

29 R. Hulst, Q. B. Broxterman, J. Kamphuis, F. Formaggio, M. Crisma, C. Toniolo, R. M. Kellogg, *Tetrahedron: Asymmetry* **1997**, *8*, 1987–1999.

30 H. J. Kim, W. R. Jackson, *Tetrahedron: Asymmetry* **1992**, *3*, 1421–1430.
31 C. E. Song, Y. J. Chun, I. O. Kim, *Synth. Commun.* **1994**, *24*, 103–109.
32 Y. Shvo, Y. Becker, M. Gal, *J. Chem. Soc., Chem. Commun.* **1994**, 2719–2720.
33 A. Mori, Y. Ikeda, K. Kinoshita, S. Inoue, *Chem. Lett.* **1989**, 2119–2122.
34 D. J. P. Hogg, M. North, R. B. Stokoe, *Tetrahedron* **1994**, *50*, 7933–7946.
35 M. North, *Tetrahedron* **1992**, *48*, 5509–5522.
36 Y. Masuda, M. Tanihara, Y. Imanishi, T. Hagashimura, *Bull. Soc. Chem. Jpn.* **1985**, *58*, 497–504.
37 H. Danda, *Synlett* **1991**, 263–264.
38 Y. Shvo, M. Gal, Y. Becker, A. Elgavi, *Tetrahedron: Asymmetry* **1996**, *7*, 911–924.
39 H. Danda, H. Nishikawa, K. Otaka, *J. Org. Chem.* **1991**, *56*, 6740–6741.
40 E. F. Kogut, J. C. Thoen, M. A. Lipton, *J. Org. Chem.* **1998**, *63*, 4604–4610.
41 W. R. Jackson, H. A. Jacobs, H. J. Kim, *Aust. J. Chem.* **1992**, *45*, 2073–2076.
42 D. Apperley, M. North, R. B. Stokoe, *Tetrahedron: Asymmetry* **1995**, *6*, 1869–1872.
43 D. Callant, B. Coussens, T. v. d. Maten, J. G. de Vries, N. K. de Vries, *Tetrahedron: Asymmetry* **1992**, *3*, 401–414.
44 D. J. P. Hogg, M. North, R. B. Stokoe, W. G. Teasdale, *Tetrahedron: Asymmetry* **1993**, *4*, 1553–1558.
45 L. Xie, W. Hua, A. S. C. Chan, Y.-C. Leung, *Tetrahedron: Asymmetry* **1999**, *10*, 4715–4728.
46 R. F. C. Brown, W. R. Jackson, T. D. McCarthy, *Tetrahedron: Asymmetry* **1993**, *4*, 2149–2150.
47 R. F. C. Brown, W. R. Jackson, T. D. McCarthy, *Tetrahedron: Asymmetry* **1993**, *4*, 205–206.
48 R. F. C. Brown, A. C. Donohue, W. R. Jackson, T. D. McCarthy, *Tetrahedron* **1994**, *50*, 13739–13752.
49 H. Danda, *Bull. Chem. Soc. Jpn.* **1991**, *64*, 3743–3745.
50 S.-K. Tian, L. Deng, *J. Am. Chem. Soc.* **2001**, *123*, 6195–6196.
51 S.-K. Tian, R. Hong, L. Deng, *J. Am. Chem. Soc.* **2003**, *125*, 9900–9901.
52 I. P. Holmes, H. B. Kagan, *Tetrahedron Lett.* **2000**, *41*, 7453–7456.
53 I. P. Holmes, H. B. Kagan, *Tetrahedron Lett.* **2000**, *41*, 7457–7460.
54 For reviews, see: (a) T. Bach, *Angew. Chem.* **1994**, *106*, 433–435; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 417–419; (b) H. Gröger, E. M. Vogl, M. Shibasaki, *Chem. Eur. J.* **1998**, *4*, 1137–1141; (c) S. G. Nelson, *Tetrahedron: Asymmetry* **1998**, *9*, 357–389; (d) T. D. Machajewski, C.-H. Wong, *Angew. Chem.* **2000**, *112*, 1406; *Angew. Chem. Int. Ed.* **2000**, *39*, 1352.
55 For selected examples of the use of aldol products in pharmaceutical research, see: A. Kleemann, J. Engels, B. Kutscher, D. Reichert, *Pharmaceutical Substances: Syntheses, Patents, Applications*, 4th edition, Thieme, Stuttgart, **2001**.
56 S. Kobayashi, Y. Fujishita, T. Mukaiyama, *Chem Lett.* **1990**, 1455–1458.
57 For selected outstanding contributions in the field of metal-catalyzed asymmetric aldol reaction, see: (a) references [74] and [75]; (b) D. A. Evans, M. C. Kozlowski, C. S. Burgey, D. W. C. MacMillan, *J. Am. Chem. Soc.* **1997**, *119*, 7893–7894 and references cited therein; (c) J. Krüger, E. M. Carreira, *J. Am. Chem. Soc.* **1998**, *120*, 837–838; (d) A. Yanagisawa, Y. Matsumoto, H. Nakashima, K. Asakawa, H. Yamamoto, *J. Am. Chem. Soc.* **1997**, *119*, 9319–9320.
58 For a very recent review, see: P. I. Dalko, L. Moisan, *Angew. Chem.* **2004**, *116*, 5248–5286; *Angew. Chem. Int. Ed.* **2004**, *43*, 5138–5175, and references cited therein.
59 A detailed summary of this work is given in: S. E. Denmark, R. A. Stavenger, *Acc. Chem. Res.* **2000**, *33*, 432–440.
60 S. E. Denmark, R. A. Stavenger, *J. Am. Chem. Soc.* **2000**, *122*, 8837–8847.
61 S. E. Denmark, R. A. Stavenger, K.-T. Wong, *J. Org. Chem.* **1998**, *63*, 918–919.
62 S. E. Denmark, R. A. Stavenger, *J. Org. Chem.* **1998**, *63*, 9524–9527.
63 (a) S. E. Denmark, S. B. Winter,

X. Su, K.-T. Wong, *J. Am. Chem. Soc.* **1996**, *118*, 7404–7405; (b) S. E. Denmark, Y. Fan, *J. Am. Chem. Soc.* **2002**, *124*, 4233–4235.
64 S. E. Denmark, S. B. Winter, *Synlett* **1997**, 1087–1089.
65 A. Ando, T. Miura, T. Tatematsu, T. Shioiri, *Tetrahedron Lett.* **1993**, *34*, 1507–1510.
66 T. Shioiri, A. Bohsako, A. Ando, *Heterocycles* **1996**, *42*, 93–97.
67 C.-T. Chen, S.-D. Chao, K.-C. Yen, C.-H. Chen, I.-C. Chou, S.-W. Hon, *J. Am. Chem. Soc.* **1997**, *119*, 11341–11342.
68 S. Kobayashi, *Kagaku Kogyo* **1989**, *42*, 245, and references cited therein.
69 B. List, R. A. Lerner, C. F. Barbas III, *J. Am. Chem. Soc.* **2000**, *122*, 2395–2396.
70 For a review about the proline-catalyzed aldol reaction, see: (a) B. List, *Synlett* **2001**, 1675–1686; (b) B. List, *Tetrahedron* **2002**, *58*, 5573–5590; (c) B. List, *Acc. Chem. Res.* **2004**, *37*, 548–557; (d) M. Movassaghi, E. N. Jacobsen, *Science* **2002**, *298*, 1904–1905.
71 K. Sakthivel, W. Notz, T. Bui, C. F. Barbas III, *J. Am. Chem. Soc.* **2001**, *123*, 5260–5267.
72 This also means that a further reaction step – deprotonation or silylation – in order to prepare the required enolates and enol ethers, respectively, can be avoided.
73 B. List, P. Pojarliev, C. Castello, *Org. Lett.* **2001**, *3*, 573–575.
74 Y. M. A. Yamada, N. Yoshikawa, H. Sasai, M. Shibasaki, *Angew. Chem.* **1997**, *109*, 1942–1944; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1871–1873.
75 N. Yoshikawa, Y. M. A. Yamada, J. Das, H. Sasai, M. Shibasaki, *J. Am. Chem. Soc.* **1999**, *121*, 4168.
76 (a) H. Torü, M. Nakadai, K. Ishihara, S. Saito, H. Yamamoto, *Angew. Chem.* **2004**, *116*, 2017–2020; *Angew. Chem. Int. Ed.* **2004**, *43*, 1983–1986; (b) A. Hartikka, P. I. Arvidsson, *Tetrahedron: Asymmetry* **2004**, *15*, 1831–1834; (c) A. Berkessel, B. Koch, J. Lex, *Adv. Synth. Catal.* **2004**, *346*, 1141–1146; (d) H. J. Martin, B. List, *Synlett* **2003**, 1901–1902.
77 A. Cordova, W. Notz, C. F. Barbas III, *J. Org. Chem.* **2002**, *67*, 301–303.
78 A. Bøgevig, N. Kumaragurubaran, K. A. Jørgensen, *Chem. Commun.* **2002**, 620–621.
79 (a) Y. Sekiguchi, A. Sasaoka, A. Shimonomoto, S. Fujioka, H. Kotsuki, *Synlett* **2003**, 1655–1658; (b) T. P. Loh, L.-C. Feng, H.-Y. Yang, J.-Y. Yang, *Tetrahedron Lett.* **2002**, *43*, 8741–8743; (c) P. Kotrusz, I. Kmentova, B. Gotov, S. Toma, E. Solcaiova, *Chem. Commun.* **2002**, 2510–2511.
80 H. Gröger, J. Wilken, *Angew. Chem.* **2001**, *113*, 545–548; *Angew. Chem. Int. Ed.* **2001**, *40*, 529–532.
81 (a) S. Saito, M. Nakadai, H. Yamamoto, *Synlett* **2001**, 1245–1248; (b) M. Nakadai, S. Saito, H. Yamamoto, *Tetrahedron* **2002**, *58*, 8167–8177; (c) For a review, see: S. Saito, H. Yamamoto, *Acc. Chem. Res.* **2004**, *37*, 570–579.
82 S. E. Denmark, S. B. D. Winter, X. Su, K.-T. Wong, *J. Am. Chem. Soc.* **1996**, *118*, 7404–7405.
83 S. E. Denmark, K.-T. Wong, R. A. Stavenger, *J. Am. Chem. Soc.* **1997**, *119*, 2333–2334.
84 S. E. Denmark, R. A. Stavenger, K.-T. Wong, X. Su, *J. Am. Chem. Soc.* **1999**, *121*, 4982–4991.
85 For a review, see: S. E. Denmark, R. A. Stavenger, *Acc. Chem. Res.* **2000**, *33*, 432–440.
86 S. E. Denmark, S. K. Gosh, *Angew. Chem.* **2001**, *113*, 4895–4898; *Angew. Chem. Int. Ed.* **2001**, *40*, 4759–4762.
87 C. M. Gasparski, M. J. Miller, *Tetrahedron* **1991**, *47*, 5367–5378.
88 M. Horikawa, J. Busch-Petersen, E. J. Corey, *Tetrahedron Lett.* **1999**, *40*, 3843–3846.
89 A. Ando, T. Miura, T. Tatematsu, T. Shioiri, *Tetrahedron Lett.* **1993**, *34*, 1507–1510.
90 For a review, see: K. Maruoka, T. Ooi, *Chem. Rev.* **2003**, *103*, 3013–3028.
91 T. Ooi, M. Taniguchi, M. Kameda, K. Maruoka, *Angew. Chem.* **2002**, *114*, 4724–4726; *Angew. Chem. Int. Ed.* **2002**, *41*, 4542–4544.
92 W. Notz, B. List, *J. Am. Chem. Soc.* **2000**, *122*, 7386–7387.

93 K. Sakthivel, W. Notz, T. Bui, C. F. Barbas III, *J. Am. Chem. Soc.* **2001**, *123*, 5260–5267.
94 (a) B. List, *Synlett* **2001**, 1675–1686; (b) B. List, P. Pojarliev, C. Castello, *Org. Lett.* **2001**, *3*, 573–575.
95 (a) A. B. Northrup, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2002**, *124*, 6798–6799; (b) R. I. Storer, D. W. C. MacMillan, *Tetrahedron* **2004**, *60*, 7705–7714; (c) N. Mase, F. Tanaka, C. F. Barbas III, *Angew. Chem.* **2004**, *116*, 2474–2477; *Angew. Chem. Int. Ed.* **2004**, *43*, 2420–2423; (d) A. Cordova, *Tetrahedron Lett.* **2004**, *45*, 3949–3952.
96 (a) S. Bahmanyar, K. N. Houk, H. J. Martin, B. List, *J. Am. Chem. Soc.* **2003**, *125*, 2475–2479; (b) For a review, see: C. Allemann, R. Gordillo, F. R. Clemente, P. H.-Y. Cheong, K. N. Houk, *Acc. Chem. Res.* **2004**, *37*, 558–569.
97 U. Eder, G. Sauer, R. Wiechert, *Angew. Chem.* **1971**, *83*, 492–493; *Angew. Chem. Int. Ed. Engl.* **1971**, *10*, 496–497.
98 U. Eder, R. Wiechert, G. Sauer (Schering AG), DE 2014757, **1971**.
99 Z. G. Hajos, D. R. Parrish (F. Hoffmann–La Roche and Co., AG), DE 2102623, **1971**.
100 Z. G. Hajos, D. R. Parrish, *J. Org. Chem.* **1974**, *39*, 1612–1615.
101 Z. G. Hajos, D. R. Parrish, *J. Org. Chem.* **1974**, *39*, 1615–1621.
102 G. S. Cortez, R. L. Tennyson, D. Romo, *J. Am. Chem. Soc.* **2001**, *123*, 7945–7946.
103 G. S. Cortez, S. H. Oh, D. Romo, *Synthesis* **2001**, 1731–1736.
104 For a review see: N. Cohen, *Acc. Chem. Res.* **1976**, *9*, 412–417.
105 T. Bui, C. F. Barbas III, *Tetrahedron Lett.* **2000**, *41*, 6951–6954.
106 C. Agami, N. Platzer, H. Sevestre, *Bull. Soc. Chim. Fr.* **1987**, *2*, 358–360.
107 C. Agami, *Bull. Soc. Chim. Fr.* **1988**, *3*, 499–507.
108 C. Agami, C. Puchot, *J. Mol. Catal.* **1986**, *38*, 341–343.
109 C. Agami, J. Levisalles, J. Puchot, *J. Chem. Soc., Chem. Commun.* **1985**, *8*, 441–442.
110 C. Girard, H. B. Kagan, *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 2922–2959, and references cited therein.
111 For a previous related work on the achiral amine-catalyzed aldol reaction, see: S. Bahmanyar, K. N. Houk, *J. Am. Chem. Soc.* **2001**, *123*, 11273–11283.
112 S. Bahmanyar, K. N. Houk, *J. Am. Chem. Soc.* **2001**, *123*, 12911–12912.
113 Y. Tamai, Y. Mitsutani, H. Uda, *J. Chem. Soc., Chem. Commun.* **1982**, 502–503.
114 Y. Tamai, H. Hagiwara, H. Uda, N. Harada, *J. Chem. Soc., Chem. Commun.* **1983**, 114–116.
115 S. Kwiatkowski, A. Syed, C. P. Brock, D. S. Watt, *Synthesis* **1989**, 818–820.
116 I. Shimizu, Y. Naito, J. Tsuji, *Tetrahedron Lett.* **1980**, *21*, 487–490.
117 S. Takano, C. Kasahara, K. Ogasawara, *J. Chem. Soc., Chem. Commun.* **1981**, 635–637.
118 S. Danishefsky, P. Cain, *J. Am. Chem. Soc.* **1975**, *97*, 5282–5283.
119 S. Danishefsky, P. Cain, *J. Am. Chem. Soc.* **1976**, *98*, 4975–4983.
120 C. Pidathala, L. Hoang, N. Vignola, B. List, *Angew. Chem.* **2003**, *115*, 2891–2894; *Angew. Chem. Int. Ed.* **2003**, *42*, 2785–2788.
121 G. Bluet, J.-M. Campagne, *J. Org. Chem.* **2001**, *66*, 4293–4298.
122 For a review about the asymmetric nitroaldol reaction, see: M. Shibasaki, H. Gröger in: *Comprehensive Asymmetric Catalysis, Volume 3*, Eds.: E. Jacobsen, A. Pfaltz, H. Yamamoto, Springer, Heidelberg, **1999**, p. 1075–1090.
123 This reaction reported by the Shibasaki group in 1992 (see also references [122], [124] and [125]) also represents the first example of the enantioselective catalytic nitroaldol reaction.
124 For some selected excellent contributions, see: (a) H. Sasai, T. Suzuki, S. Arai, T. Arai, M. Shibasaki, *J. Am. Chem. Soc.* **1992**, *114*, 4418–4420; (b) H. Sasai, T. Suzuki, N. Itoh, S. Arai, M. Shibasaki, *Tetrahedron Lett.* **1993**, *34*, 2657–2660; (c) H. Sasai, Y. M. A. Yamada, T. Suzuki, M. Shibasaki, *Tetrahedron*

1994, *50*, 12313–12318; (d) H. Sasai, T. Tokunaga, S. Watanabe, T. Suzuki, N. Itoh, M. Shibasaki, *J. Org. Chem.* **1995**, *60*, 7388–7389.
125 For a review about the applications of the multifunctional catalysts developed by the Shibasaki group, see: M. Shibasaki, H. Sasai, T. Arai, *Angew. Chem.* **1997**, *109*, 1290–1310; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1236–1256.
126 R. Chinchilla, C. Nájera, P. Sánchez-Agullo, *Tetrahedron: Asymmetry* **1994**, *5*, 1393–1402.
127 Y. Misumi, R. A. Bulman, K. Matsumoto, *Heterocycles* **2002**, *56*, 599–605.
128 E. J. Corey, F.-Y. Zang, *Angew. Chem.* **1999**, *111*, 2057–2059; *Angew. Chem. Int. Ed. Engl.* **1999**, *38*, 1931–1934.
129 E. J. Corey, F. Xu, M. C. Noe, *J. Am. Chem. Soc.* **1997**, *119*, 12414–12415.
130 E. J. Corey, Y. Bo, J. Busch-Petersen, *J. Am. Chem. Soc.* **1998**, *120*, 13000–13001.
131 E. J. Corey, M. C. Noe, F. Xu, *Tetrahedron Lett.* **1998**, *39*, 5347–5350.
132 A. Bøgevig, K. V. Gothelf, K. A. Jørgensen, *Chem. Eur. J.* **2002**, *8*, 5652–5661.
133 A. Bøgevig, T. B. Poulsen, W. Zhuang, K. A. Jørgensen, *Synlett* **2003**, 1915–1918.
134 H. Wynberg, *Top. Stereochem.* **1986**, *16*, 87–130.
135 For a general review about methods for the synthesis of optically active *β*-lactones, see: H. W. Yang, D. Romo, *Tetrahedron* **1999**, *55*, 6403–6434; (b) For a selected recent chiral metal complex-catalyzed asymmetric approach, see: S. G. Nelson, Z. Wan, *Org. Lett.* **2000**, *2*, 1883–1886.
136 D. Borrmann, R. Wegler, *Chem. Ber.* **1967**, *100*, 1575–1579.
137 H. Wynberg, E. G. J. Staring, *J. Am. Chem. Soc.* **1982**, *104*, 166–168.
138 G. S. Cortez, R. L. Tennyson, D. Romo, *J. Am. Chem. Soc.* **2001**, *123*, 7945–7946.
139 H. Wynberg, E. G. J. Staring, *J. Org. Chem.* **1985**, *50*, 1977–1979.
140 P. E. F. Ketelaar, E. G. J. Staring, H. Wynberg, *Tetrahedron Lett.* **1985**, *26*, 4665–4668.
141 C. E. Song, T. H. Ryu, E. J. Roh, I. O. Kim, H.-J. Ha, *Tetrahedron: Asymmetry* **1994**, *5*, 1215–1218.
142 (a) R. Tennyson, D. Romo, *J. Org. Chem.* **2000**, *65*, 7248–7252; (b) C. Zhu, X. Shen, S. G. Nelson, *J. Am. Chem. Soc.* **2004**, *126*, 5352–5353.
143 (a) K. Morita, T. Kobayashi, *Bull. Chem. Soc. Jpn.* **1969**, *42*, 2732; (b) B. Baylis, M. E. D. Hillman, DE-B 2155113, **1972** [CA **1972**, *77*, 34174q].
144 For a brief review of recent developments in the asymmetric Baylis–Hillman reaction, see: P. Langer, *Angew. Chem.* **2000**, *112*, 3177–3180; *Angew. Chem. Int. Ed.* **2000**, *39*, 3049–3052.
145 E. Ciganek, *Org. React.* **1977**, *51*, 201–350.
146 (a) D. Basavaiah, A. J. Rao, T. Satyanatayana, *Chem. Rev.* **2003**, *103*, 811–891; (b) D. Basavaiah, P. D. Rao, R. S. Hyma, *Tetrahedron* **1996**, *52*, 8001–8062.
147 S. E. Drewes, G. H. P. Roos, *Tetrahedron* **1988**, *44*, 4653–4670.
148 H. M. R. Hoffmann, J. Rabe, *Angew. Chem.* **1985**, *97*, 96–112; *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 94–109.
149 N. S. Isaacs, A. Gilbert, T. W. Heritage, *Tetrahedron: Asymmetry* **1991**, *2*, 969–972.
150 L. J. Brzezinski, S. Rafel, J. W. Leahy, *J. Am. Chem. Soc.* **1997**, *119*, 4317–4318.
151 I. E. Markó, P. R. Giles, N. J. Hindley, *Tetrahedron* **1997**, *53*, 1015–1024.
152 T. Oishi, H. Oguri, M. Hirama, *Tetrahedron: Asymmetry* **1995**, *6*, 1241–1244.
153 A. G. M. Barrett, A. S. Cook, A. Kamimura, *Chem. Commun.* **1998**, 2533–2534.
154 (a) Y. Iwabuchi, M. Nakatani, N. Yokoyama, S. Hatakeyama, *J. Am. Chem. Soc.* **1999**, *121*, 10219–10220; (b) M. Shi, J.-K. Jiang, *Tetrahedron: Asymmetry* **2002**, *13*, 1941–1947; (c) M. Shi, J.-K. Jiang, C.-Q. Li, *Tetrahedron Lett.* **2002**, *43*, 127–130; (d) J. E. Imbriglio, M. M. Vasbinder, S. J. Miller, *Org. Lett.* **2003**, *5*, 3741–3743.
155 M. Shi, Y.-M. Xu, *Angew. Chem.* **2002**, *114*, 4689–4692; *Angew. Chem. Int. Ed.* **2002**, *41*, 4507–4510.

156 F. Roth, P. Gygax, G. Frater, *Tetrahedron Lett.* **1992**, *33*, 1045–1048.
157 T. Hayase, T. Shibata, K. Soai, Y. Wakatsuki, *Chem. Commun.* **1998**, 1271–1272.
158 N. T. McDougal, S. E. Schaus, *J. Am. Chem. Soc.* **2003**, *125*, 12094–12095.
159 T. Iwama, H. Kinoshita, T. Kataoka, *Tetrahedron Lett.* **1999**, *40*, 3741–3744.
160 (a) L. M. Walsh, C. L. Winn, J. M. Goodman, *Tetrahedron Lett.* **2002**, *43*, 8219–8222; (b) For examples of asymmetric MBH reactions (up to 74% ee) involving $TiCl_4$ and chiral thioethers catalysts, see: T. Kataoka, T. Iwama, S. Tsujiyama, K. Kanematsu, T. Iwamura, S. Watanabe, *Chem. Lett.* **1999**, 257–258.
161 A. G. M. Barrett, A. Kamimura, *J. Chem. Soc., Chem. Commun.* **1995**, 1755–1756.
162 For comprehensive reviews about asymmetric allylation reactions, see: (a) Y. Yamamoto, N. Asao, *Chem. Rev.* **1993**, *93*, 2207; (b) S. E. Denmark, N. G. Almstead in: *Modern Carbonyl Chemistry* (Ed.: J. Otera), Wiley–VCH, Weinheim, **2000**, chapter 10.
163 For a review, see: A. Yanagisawa in: Comprehensive Asymmetric Catalysis (Eds.: E. Jacobsen, A. Pfaltz, H. Yamamoto), Vol. 2, Springer, Heidelberg, **1999**, chapter 27.
164 For a recent summary of the Lewis-base-catalyzed allylation with a main focus on phosphoramide catalysts, see: S. E. Denmark, J. Fu, *Chem. Commun.* **2003**, 167–170.
165 S. E. Denmark, D. M. Coe, N. E. Pratt, B. D. Griedel, *J. Org. Chem.* **1994**, *59*, 6161–6163.
166 S. E. Denmark, J. Fu, *J. Am. Chem. Soc.* **2000**, *122*, 12021–12022.
167 S. E. Denmark, J. Fu, *J. Am. Chem. Soc.* **2001**, *123*, 9488–9489.
168 S. E. Denmark, J. Fu, *Org. Lett.* **2002**, *4*, 1951–1953.
169 S. E. Denmark, J. Fu, *J. Am. Chem. Soc.* **2003**, *125*, 2208–2216.
170 K. Iseki, Y. Kuroki, M. Takahashi, Y. Kobayashi, *Tetrahedron Lett.* **1996**, *37*, 5149–5150.
171 K. Iseki, Y. Kuroki, M. Takahashi, S. Kishimoto, Y. Kobayashi, *Tetrahedron* **1997**, *53*, 3513–3526.
172 J. Hellwig, T. Belser, J. F. K. Müller, *Tetrahedron Lett.* **2001**, *42*, 5417–5419.
173 K. Iseki, S. Mizuno, Y. Kuroki, Y. Kobayashi, *Tetrahedron Lett.* **1998**, *39*, 2767–2770.
174 K. Iseki, S. Mizuno, Y. Kuroki, Y. Kobayashi, *Tetrahedron* **1999**, *55*, 977–988.
175 R. M. Angell, A. G. M. Barrett, D. C. Braddock, S. Swallow, B. D. Vickery, *Chem. Commun.* **1997**, 919–920.
176 M. Nakajima, M. Saito, M. Shiro, S.-i. Hashimoto, *J. Am. Chem. Soc.* **1998**, *120*, 6419–6420.
177 See, for example: K. Sato, M. Kira, H. Sakurai, *Tetrahedron Lett.* **1989**, *30*, 4375–4378.
178 A. V. Malkov, M. Orsini, D. Pernazza, K. W. Muir, V. Langer, P. Meghani, P. Kocovsky, *Org. Lett.* **2002**, *4*, 1047–1049.
179 A. V. Malkov, M. Bell, M. Vasieu, V. Bugatti, P. Kocovsky, *J. Mol. Cat. A* **2003**, *196*, 179–186.
180 A. V. Malkov, L. Dufkova, L. Farrugia, P. Kocovsky, *Angew. Chem.* **2003**, *115*, 3802–3805; *Angew. Chem. Int. Ed.* **2003**, *42*, 3674–3677.
181 T. Shimida, A. Kina, S. Ikeda, T. Hayashi, *Org. Lett.* **2002**, *4*, 2799–2801.
182 For a review, see: K. Soai, T. Shibata in: *Comprehensive Asymmetric Catalysis* (Eds.: E. Jacobsen, A. Pfaltz, H. Yamamoto), Volume 2, Springer, Heidelberg, **1999**, p. 911–922.
183 For selected examples, see: (a) J.-P. Barnier, L. Blanco, G. Rousseau, E. Guibe-Jampel, *J. Org. Chem.* **1993**, *58*, 1570–1574; (b) J. F. Coope, B. G. Main, *Tetrahedron: Asymmetry* **1995**, *6*, 1393–1398; (c) S.-T. Chen, J. M. Fang, *J. Org. Chem.* **1997**, *62*, 4349–4357.
184 For selected examples, see: (a) D. Seebach, B. Weber, *Angew. Chem.* **1992**, *104*, 96–97; *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 84; (b) K. Tomioka, M. Nakajima, K. Koga, *Tetrahedron* **1993**, *49*, 9751–9758.
185 K. Iseki, T. Nagai, Y. Kobayashi, *Tetrahedron Lett.* **1994**, *35*, 3137–3138.
186 G. K. S. Prakash, R. Krishnamurti, G. A. Olah, *J. Am. Chem. Soc.* **1989**, *111*, 393–395.

187 R. Krishnamurti, D. R. Bellew, G. K. S. Prakash, *J. Org. Chem.* **1991**, *56*, 984–989.

188 (a) M. Ballester, *Chem. Rev.* **1955**, *55*, 283; (b) G. Berti, *Top. Stereochem.* **1973**, *7*, 93–251.

189 T. Rosen, Comp. *Org. Syn.* **1991**, *2*, 409–439.

190 S. Colonna, R. Fornasier, U. Pfeiffer, *J. Chem. Soc., Perkin Trans. 1* **1978**, 8–11.

191 J. C. Hummelen, H. Wynberg, *Tetrahedron Lett.* **1978**, 1089–1092.

192 (a) P. Bakó, A. Szöllosy, P. Bombicz, L. Töke, *Synlett* **1997**, 291–292; (b) P. Bakó, K. Vizvárdi, Z. Bajor, L. Töke, *J. Chem. Soc., Chem. Commun.* **1998**, 1193–1194; (c) P. Bakó, K. Vizvárdi, S. Toppet, E. Van der Eycken, G. J. Hoornaert, L. Töke, *Tetrahedron* **1998**, *54*, 14975–14988; (d) P. Bakó, E. Czinege, T. Bakó, M. Czugler, L. Töke, *Tetrahedron: Asymmetry* **1999**, *10*, 4539–4551.

193 S. Arai, T. Shiori, *Tetrahedron Lett.* **1998**, *39*, 2145–2148.

194 (a) S. Arai, Y. Shirai, T. Ishida, T. Shiori, *J. Chem. Soc., Chem. Commun.* **1999**, 49–50; (b) S. Arai, Y. Shirai, T. Ishida, T. Shiori, *Tetrahedron* **1999**, *55*, 6375–6386.

195 S. Arai, T. Ishida, T. Shiori, *Tetrahedron Lett.* **1998**, *39*, 8299–8302.

196 S. Arai, T. Shiori, *Tetrahedron* **2002**, *58*, 1407–1413.

197 Colonna et al. reported that up to 62% ee can be achieved when the *Darzens* condensation of aromatic aldehydes with phenacyl chlorides is carried out in the presence of bovine serum albumin: R. Annunziata, S. Banfi, S. Colonna, *Tetrahedron Lett.* **1985**, *26*, 2471–2474.

198 For reviews on the use of sulfur-ylides for the synthesis of epoxides, see: (a) B. M. Trost, L. S. Melvon, *Sulfur Ylides*, Academic Press, New York, **1975**; (b) J. Aube in: *Comprehensive Organic Synthesis* (Eds.: B. M. Trost, I. Fleming), Pergamon Press, New York, **1991**, p. 819–825.

199 Alternatively, chiral epoxides can be prepared efficiently by other routes, in particular asymmetric epoxidation of alkenes. For related reviews in this field, see: (a) T. Katsuki in: *Comprehensive Asymmetric Catalysis I–III* (Eds.: Jacobsen, E. N.; Pfaltz, A.; Yamamoto H.), Springer, Berlin, **1999**, p. 621f.; (b) E. N. Jacobsen, M. H. Wu in: *Comprehensive Asymmetric Catalysis I–III* (Eds.: Jacobsen, E. N.; Pfaltz, A.; Yamamoto H.), Springer, Berlin, **1999**, p. 649f.; (c) For organocatalytic asymmetric epoxidations, see chapter 10.

200 For an excellent review in this field, see: A.-H. Li, L.-X. Dai, V. K. Aggarwal, *Chem. Rev.* **1997**, *97*, 2341–2372.

201 N. Furukawa, Y. Sugihara, H. Fujihara, *J. Org. Chem.* **1989**, *54*, 4222–4224.

202 It should be mentioned at this stage that in addition to the catalytic version, numerous sulfur-ylide mediated asymmetric diastereoselective epoxidations which require the use of stoichiometric amounts of the sulfur-ylide were reported. In these cases, the sulfonium salts had to be prepared in a first step, and were used in a subsequent diastereoselective epoxidation step. For some selected references for this type of stoichiometric asymmetric two-step epoxidation, see: (a) T. Durst, L. Breau, R. N. Ben, *Phosphorus Sulfur* **1993**, *74*, 215–232; (b) A. Solladie-Cavallo, A. Adib, *Tetrahedron* **1992**, *48*, 2453–2464; (c) A. Solladie-Cavallo, A. Diep-Vohuule, *J. Org. Chem.* **1995**, *60*, 3494–3498; (d) A. Solladie-Cavallo, A. Diep-Vohuule, V. Sunjic, V. Vinkovic, *Tetrahedron: Asymmetry* **1996**, *7*, 1783–1788; (e) Y.-G. Zhou, X.-L. Hou, L.-X. Dai, L.-J. Xia, M.-H. Tang, *J. Chem. Soc., Perkin Trans 1* **1999**, 77–80; (f) A. Solladie-Cavallo, M. Roje, T. Isarno, V. Sunjic, V. Vinkovic, *Eur. J. Org. Chem.* **2000**, 1077–1080.

203 A.-H. Li, L.-X. Dai, X.-L. Hou, Y.-Z. Huang, F.-W. Li, *J. Org. Chem.* **1996**, *61*, 489–493.

204 T. Saito, D. Akiba, M. Sakairi, S. Kanazawa, *Tetrahedron Lett.* **2001**, *42*, 57–59.

205 K. Julienne, P. Metzner, *J. Org. Chem.* **1998**, *63*, 4532–4534.

206 K. Julienne, P. Metzner, V. Henryon, *J. Chem. Soc., Perkin Trans. 1* **1999**, 731–736.

207 J. Zanardi, C. Leriverend, D. Aubert, K. Julienne, P. Metzner, *J. Org. Chem.* **2001**, *66*, 5620–5623.

208 J. Zanardi, D. Lamazure, S. Miniere, V. Reboul, P. Metzner, *J. Org. Chem.* **2002**, *67*, 9083–9086.

209 C. L. Winn, B. R. Bellenie, J. M. Goodman, *Tetrahedron Lett.* **2002**, *43*, 5427–5430.

210 J. M. Goodman, B. R. Bellenie, Abstracts of Papers, 225th ACS National Meeting, New Orleans, United States, March 23–27, **2003**.

211 R. Hayakawa, M. Shimizu, *Synlett* **1999**, 1328–1330.

212 V. K. Aggarwal in: *Comprehensive Asymmetric Catalysis I–III* (Eds.: Jacobsen, E. N.; Pfaltz, A.; Yamamoto H.), Springer, Berlin, **1999**, p. 679–693.

213 For a review about the development of the sulfur-ylide chemistry in the Aggarwal group, see: V. K. Aggarwal, *Synlett* **1998**, 329–336.

214 V. K. Aggarwal, H. Abdel-Rahmann, R. V. H. Jones, H. Y. Lee, B. D. Reid, *J. Am. Chem. Soc.* **1994**, *116*, 5973–5974.

215 V. K. Aggarwal, M. Kalomiri, A. P. Thomas, *Tetrahedron: Asymmetry* **1994**, *5*, 723–730.

216 V. K. Aggarwal, A. Thompson, R. V. H. Jones, M. Standen, *Tetrahedron: Asymmetry* **1995**, *6*, 2557–2564.

217 V. K. Aggarwal, H. Abdel-Rahmann, F. Li, R. V. H. Jones, M. Standen, *Chem. Eur. J.* **1996**, *2*, 212–218.

218 V. K. Aggarwal, J. G. Ford, A. Thompson, R. V. H. Jones, M. Standen, *J. Am. Chem. Soc.* **1996**, *118*, 7004–7005.

219 V. K. Aggarwal, J. G. Ford, S. Fonquerna, H. Adams, R. V. H. Jones, R. Fieldhouse, *J. Am. Chem. Soc.* **1998**, *120*, 8328–8339.

220 V. K. Aggarwal, L. Bell, M. P. Coogan, P. Jubault, *J. Chem. Soc., Perkin Trans 1* **1998**, 2037–2042.

221 V. T. Myllymäki, M. K. Lindvall, A. M. P. Koskinen, *Tetrahedron* **2001**, *57*, 4629–4635.

222 R. Imashiro, T. Yamanaka, M. Seki, *Tetrahedron: Asymmetry* **1999**, *10*, 2845–2851.

223 V. K. Aggarwal, E. Alonso, G. Hynd, K. M. Lydon, M. J. Palmer, M. Porcelloni, J. R. Studley, *Angew. Chem.* **2001**, *113*, 1479–1482; *Angew. Chem., Int. Ed.* **2001**, *40*, 1430–1433.

224 V. K. Aggarwal, R. Angelaud, D. Bihan, P. Blackburn, R. Fieldhouse, S. J. Fonquerna, G. D. Ford, G. Hynd, E. Jones, R. V. H. Jones, P. Jubault, M. J. Palmer, P. D. Ratcliffe, H. Adams, *J. Chem. Soc., Perkin Trans 1* **2001**, 2604–2622.

225 M. Catasus, A. Moyana, V. K. Aggarwal, *Tetrahedron Lett.* **2002**, *43*, 3475–3479.

226 For a review about the factors that influence the stereocontrol, see: V. K. Aggarwal, J. Richardson, *Chem. Commun.* **2003**, 2644–2651.

227 V. K. Aggarwal, S. Calamai, J. G. Ford, *J. Chem. Soc., Perkin Trans 1* **1997**, 593–600.

228 V. K. Aggarwal, J. N. Harvey, J. Richardson, *J. Am. Chem. Soc.* **2002**, *124*, 5747–5756.

229 F. Volatron, O. Eisenstein, *J. Am. Chem. Soc.* **1987**, *109*, 1–4.

230 (a) M. K. Lindvall, A. P. M. Koskinen, *J. Org. Chem.* **1999**, *64*, 4595–4606; (b) See also reference [24].

231 (a) W. S. Ide, J. S. Buck, *Org. React.* **1948**, *4*, 269–304; (b) H. Stetter, H. Kuhlmann, *Org. React.* **1991**, *40*, 407–496.

232 The use of cyanide in combination with chiral phase-transfer catalysts afforded up to 23% ee in the condensation of benzaldehyde: J. Castells, E. Dunach, *Chem. Lett.* **1984**, 1859–1860.

233 H. Dugas, "Bioorganic Chemistry", Springer, New York (1996), pp. 560–574.

234 R. Breslow, *J. Am. Chem. Soc.* **1958**, *80*, 3719–3726.

235 T. Ukai, R. Tanaka, T. Dokawa, *J. Pharm. Soc. Jpn.* **1943**, *63*, 293–300 (CA: **1951**, *45*, 5148e).

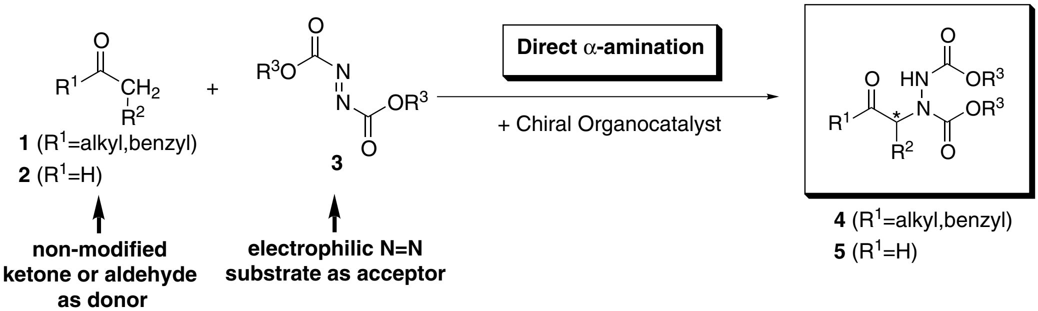
236 T. Ukai, T. Dokawa, S. Tsubokawa, *J. Pharm. Soc. Jpn.* **1944**, *64*, 3–4 (CA: **1951**, *45*, 8513e).

237 D. Enders, K. Breuer *in* "Comprehensive Asymmetric Catalysis" (E. N. Jacobsen, A. Pfaltz, H. Yamamoto, Eds.), Springer, Berlin (1999), pp. 1093–1102.
238 J. Sheehan, D. H. Hunnemann, *J. Am. Chem. Soc.* **1966**, *88*, 3666–3667.
239 J. Sheehan, T. Hara, *J. Org. Chem.* **1974**, *39*, 1196–1199.
240 W. Tagaki, Y. Tamura, Y. Yano, *Bull. Chem. Soc. Jpn.* **1980**, *53*, 478–480.
241 C. Zhao, S. Chen, P. Wu, Z. Wen, *Huaxue Xuebao* **1988**, *46*, 784–790 (CA: **1989**, *110*, 192696r).
242 (a) R. L. Knight, F. J. Leeper, *Tetrahedron Lett.* **1997**, *38*, 3611–3614; (b) A. U. Gerhard, F. J. Leeper, *Tetrahedron Lett.* **1997**, *38*, 3615–3618.
243 C. A. Dvorak, V. H. Rawal, *Tetrahedron Lett.* **1998**, *39*, 2925–2928.
244 J. Martí, J. Castells, F. López-Calahorra, *Tetrahedron Lett.* **1993**, *34*, 521–524.
245 For a recent study by *Benaglia et al.* on chiral benzimidazolium and thiazolium salts, affording up to 15% ee in the condensation of benzaldehyde, see: S. Orlandi, M. Caporale, M. Benaglia, R. Annunziata, *Tetrahedron: Asymmetry* **2003**, *14*, 3827–3830.
246 (a) J. H. Teles, J.-P. Melder, K. Ebel, R. Schneider, E. Gehrer, W. Harder, S. Brode, D. Enders, K. Breuer, G. Raabe, *Helv. Chim. Acta* **1996**, *79*, 61–83; (b) J. H. Teles, J.-P. Melder, E. Gehrer, W. Harder, K. Ebel, C. Gröning, R. Meyer, EP 0 587 044 B1, **1994** (CA: **1996**, *125*, 57906).
247 D. Enders, K. Breuer, J. H. Teles, *Helv. Chim. Acta* **1996**, *79*, 1217–1221.
248 R. L. Knight, F. J. Leeper, *J. Chem. Soc., Perkin Trans. 1* **1998**, 1891–1893.
249 D. Enders, U. Kallfass, *Angew. Chem.* **2002**, *114*, 1822–1824; *Angew. Chem. Int. Ed.* **2002**, *41*, 1743–1745.
250 K. Ebel, R. Schneider, J.-P. Melder, J. H. Teles, WO 96/02484, **1996** (CA: **1996**, *124*, 288773).
251 K. Breuer, Ph.D. thesis, Technical University of Aachen, Germany (1997).
252 D. Enders, K. Breuer, G. Raabe, J. Runsink, J. H. Teles, J.-P. Melder, K. Ebel, S. Brode, *Angew. Chem.* **1995**, *107*, 1119–1122; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1021–1024.
253 D. Enders, K. Breuer, J. Runsink, J. H. Teles, *Liebigs Ann.* **1996**, 2019–2028.
254 (a) D. Enders, K. Breuer, J. Runsink, J. H. Teles, *Helv. Chim. Acta* **1996**, *79*, 1899–1902; (b) J. H. Teles, D. Enders, K. Breuer, DE 196 29 523 A1, **1998** (CA: **1998**, *128*, 140289).
255 M. S. Kerr, J. Read de Alaniz, T. Rovis, *J. Am. Chem. Soc.* **2002**, *124*, 10298–10299.
256 M. S. Kerr, T. Rovis, *Synlett* **2003**, 1934–1936.
257 D. Enders, Enzyme-mimetic C–C- and C–N-Bond Formations *in* "Stereoselective Synthesis" (E. Ottow, K. Schöllkopf, B. G. Schulz, Eds.), Springer, New York (1994), pp. 63.
258 For a review of asymmetric catalytic approaches to α-hydroxy and α-amino phosphonates, see: H. Gröger, B. Hammer, *Chem. Eur. J.* **2000**, *6*, 943–948.
259 (a) T. Yokomatsu, T. Yamagishi, S. Shibuya, *Tetrahedron: Asymmetry* **1993**, *4*, 1779–1782; (b) T. Yokomatsu, T. Yamagishi, S. Shibuya, *Tetrahedron: Asymmetry* **1993**, *4*, 1783–1784; (c) T. Yokomatsu, T. Yamagishi, S. Shibuya, *J. Chem. Soc., Perkin Trans I* **1997**, 1527–1533; (d) N. P. Rath, C. D. Spilling, *Tetrahedron Lett.* **1994**, *35*, 227–230.
260 (a) H. Sasai, M. Bougauchi, T. Arai, M. Shibasaki, *Tetrahedron Lett.* **1997**, *38*, 2717–2720; (b) T. Arai, M. Bougauchi, H. Sasai, M. Shibasaki, *J. Org. Chem.* **1996**, *61*, 2926–2927.
261 H. Wynberg, A. A. Smaardijk, *Tetrahedron Lett.* **1983**, *24*, 5899–5900.
262 A. A. Smaardijk, S. Noorda, F. van Bolhuis, H. Wynberg, *Tetrahedron Lett.* **1985**, *26*, 493–496.

7
Nucleophilic Addition to Unsaturated Nitrogen

7.1
Nucleophilic Addition to N=N Double Bonds

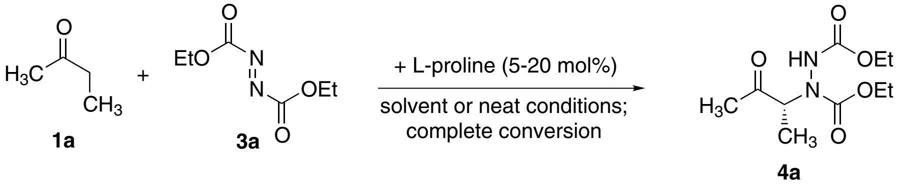
In contrast with the large number of addition reactions to C=O, and C=N double bonds, only a few examples of nucleophilic addition to N=N double bonds have been investigated [1]. In particular, asymmetric syntheses using N=N components as electrophiles have been rarely developed, despite the remarkable potential of this type of reaction [2–4]. For example, the metal-catalyzed addition of 2-keto esters to azodicarboxylates furnished chiral β-amino α-hydroxy esters which are pharmaceutically important intermediates [4b]. Several interesting asymmetric organocatalytic reactions based on use of azodicarboxylates as N=N electrophiles have been reported very recently [5–8]. These contributions, which are summarized below, emphasized the high suitability of chiral organocatalysts for these α-amination reactions of ketones and aldehydes. The basic reaction scheme is shown in Scheme 7.1. The resulting products of type **4** or **5** bearing an α-amido carbonyl framework are of interest for the preparation of a wide variety of important chiral building blocks, e.g. α-amino acids and β-amino alcohol derivatives.



Scheme 7.1

To start with the α-amination of ketones, the Jørgensen group reported a highly enantioselective addition of ketones, **1**, to azodicarboxylates, **3**, as N=N component [5]. The L amino acid L-proline was found to be a highly efficient catalyst. In a first screening using a model reaction (Scheme 7.2) it was found that diethyl

Asymmetric Organocatalysis. Albrecht Berkessel and Harald Gröger
Copyright © 2005 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim
ISBN: 3-527-30517-3



Solvent[a)]	Cat. amount [mol%]	React. time for full conv. [h]	ee [%]
Acetonitrile	20	52	96
Dichloromethane	20	76	91
Neat	20	65	92
Neat	5	65	93

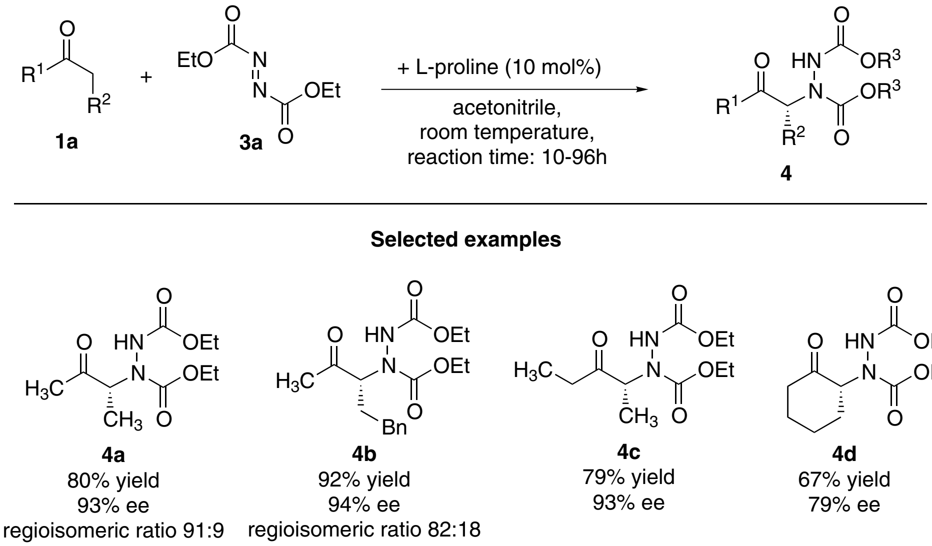
a) under neat conditions, 2 equiv. of ketone were used.

Scheme 7.2

azodicarboxylate was a more promising N=N substrate than its *iso*-propyl and *tert*-butyl analogs (for which enantioselectivity was lower). In addition, the highest enantioselectivity was obtained when acetonitrile was used as a solvent (Scheme 7.2). Dichloromethane, e.g., led to substantially lower yields and ee. It is worthy of note that the reactions can also be conducted efficiently in the absence of a solvent. For such a reaction under neat conditions higher yields and comparable enantioselectivity of up to 93% ee were observed, even when the amount of catalyst was reduced to 5 mol% [5].

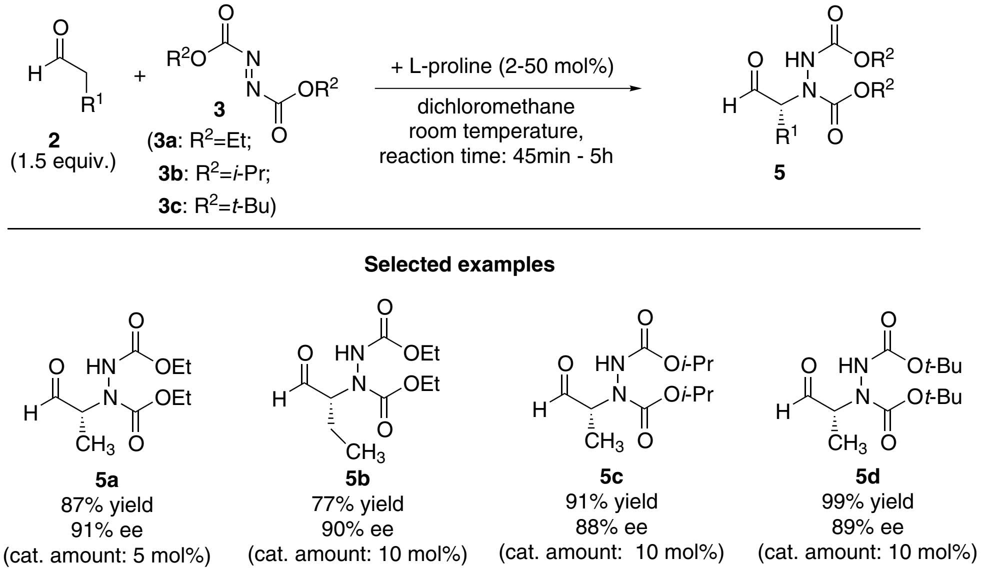
Under optimized conditions the organocatalytic α-amination has been performed successfully with a broad range of ketones, as shown in Scheme 7.3. In the presence of 10 mol% L-proline as catalyst the α-amination proceeds with formation of the desired products **4** in high yields (up to 92%) and with good to excellent enantioselectivity in the range 79–99% ee for the isolated products (selected examples are shown in Scheme 7.3) [5]. Good regioselectivity is also observed. The ratio of the two types of regioisomeric compound is in the range 76:24 to 91:9. Another advantage of this L-proline-catalyzed α-amination is the simplicity of the reaction. It can be conducted at room temperature and is based on the use of an inexpensive and readily available catalyst. Isolation by extraction after addition of water is also very practical.

Extension of this proline-catalyzed α-amination to the use of aldehydes as starting materials has been described independently by the Jørgensen and List groups [6, 7]. The principle of the reaction and some representative examples are shown in Scheme 7.4. The practicability is high – comparable with that of the analogous reaction with ketones described above. For example, in the presence of 5 mol% L-proline as catalyst propanal reacts with azodicarboxylate **3a** at room temperature in dichloromethane with formation of the α-aminated product **5a** in 87% yield and with 91% ee [7]. Good yields and high enantioselectivity can be also obtained by use of other types of solvent, e.g. toluene and acetonitrile. The products of type **5** were isolated simply by addition of water, extraction with ether, and subsequent evaporation.

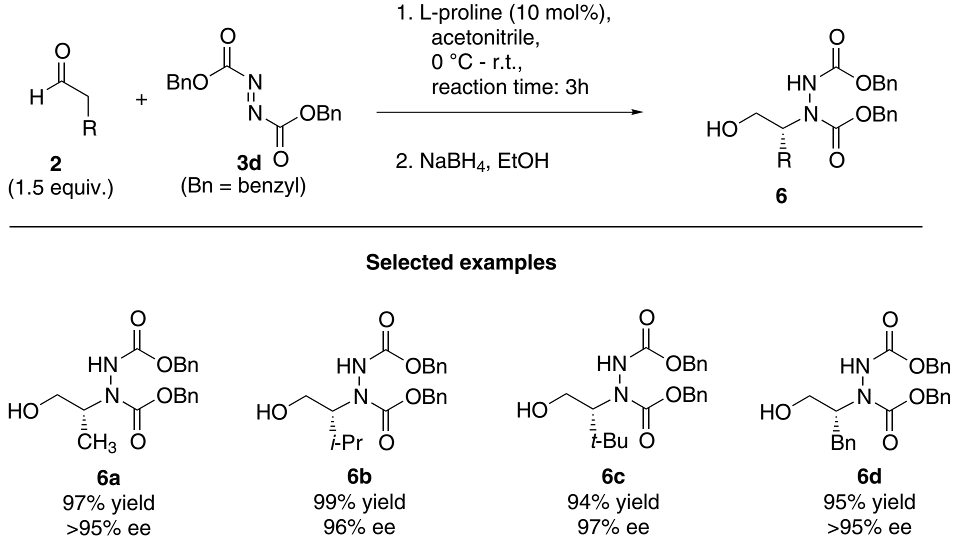


Scheme 7.3

The reaction also proceeds efficiently when smaller amounts of catalyst are used. For example, the analogous synthesis of **5a** gave 92% yield and 84% ee in the presence of only 2 mol% L-proline (compared with 93% yield and 92% ee with 50 mol% catalyst) [7]. This reaction has already been performed on a gram scale.



Scheme 7.4



Scheme 7.5

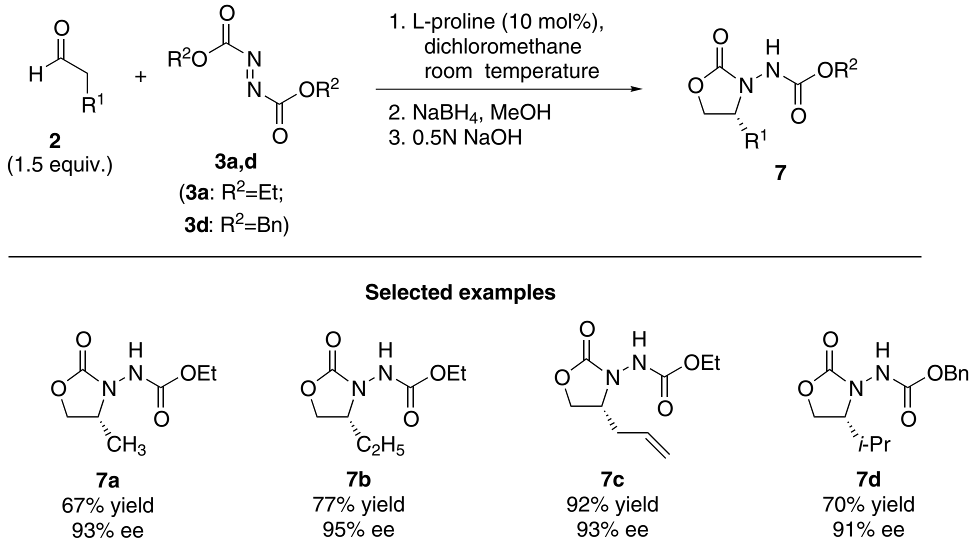
One drawback, however, is that the products **5** are unstable during extended storage towards racemization. This can be circumvented by converting the aldehydes **5** *in situ* into derivatives. Depending on the reaction conditions amino alcohols **6** or oxazolidinones **7** are obtained; these also are valuable intermediates. The two types of reductive modification are shown in Schemes 7.5 and 7.6, respectively. Such *in situ* reductions are performed by treatment with sodium borohydride.

The List group synthesized a broad variety of *N*-protected amino alcohols **6** by proline-catalyzed α-amination of aldehydes (Scheme 7.5) [6]. Under optimized conditions, the desired products of type **6** were obtained in high yields (93–99%) and with excellent enantioselectivity (up to >95% ee). Acetonitrile was found to be the preferred solvent and a catalytic amount (10 mol%) of proline was used.

The α-amination of aldehydes and subsequent reduction to form oxazolidinones (Scheme 7.6) was developed by the Jørgensen group [7]. In the presence of 10 mol% L-proline as catalyst a variety of aldehydes reacted with azodicarboxylates, **3a** and **3a**, affording the oxazolidinones **7** after subsequent reduction with borohydride and cyclization. Selected examples of the synthesis of products **7**, which were obtained in yields up to 92% and with enantioselectivity up to 95% ee, are shown in Scheme 7.6.

Several transformations of **6** and **7** were also conducted successfully [6, 7]. For example, oxidation of the aldehyde group of the *N*-protected amino aldehydes **7** and subsequent standard transformations lead to non-proteinogenic optically active α-amino acid esters [7].

With regard to the mechanism of the α-amination step, the stereochemistry has been explained on the basis of a transition state involving a proline–enamine struc-



Scheme 7.6

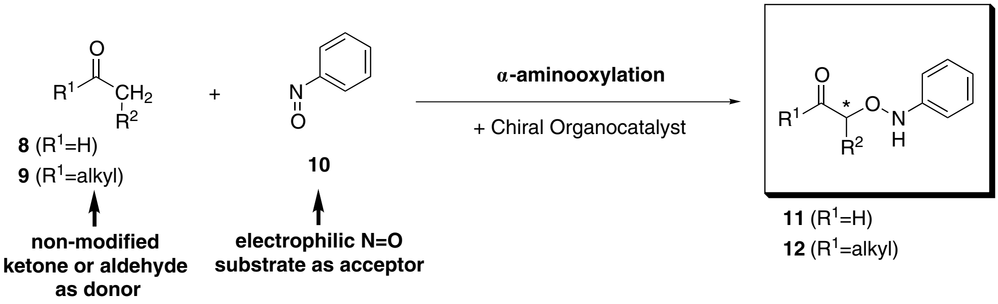
ture. This proposed transition state is analogous to those calculated by Houk et al. for the intramolecular aldol reaction [9a] and proposed for intermolecular aldol and Mannich reactions [9b].

In conclusion, the organocatalytic asymmetric α-amination of aldehydes and ketones using proline as catalyst is a new and attractive access to optically active *N*-protected α-amino aldehydes and ketones and related derivatives, e.g. α-amino acid esters.

7.2 Nucleophilic Addition to N=O Double Bonds

In addition to nucleophilic addition to N=N double bonds, very recently the MacMillan group, the Hayashi group, Zhong, and the Cordova group independently demonstrated that additions of aldehydes to the N=O double bond also are catalyzed by organocatalysts [10–13]. Nitrosobenzene was used as the N=O compound and L-proline as the organocatalyst. This asymmetric α-aminooxylation is useful for synthesis of α-hydroxyaldehydes and α-hydroxyketones, which are versatile intermediates in many organic transformations [14]. It is worthy of note that the carbonyl component can be used directly without prior modification, which simplifies the process. This reaction has also been found to proceed highly enantioselectively. The concept of the reaction is shown below in Scheme 7.7 [10–13].

It should be added that an analogous, previously developed [15], metal-catalyzed synthesis, based on use of BINAP–AgOTf as catalyst, is also available. This effi-

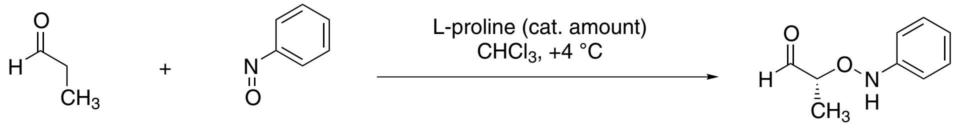


Scheme 7.7

cient route, developed by Yamamoto et al., is highly enantioselective in the presence of tin enolates of ketones as donors [15].

The MacMillan group initially conducted this α-aminooxylation of nitrosobenzene in different solvents using propanal as aldehyde in the presence of 10 mol% L-proline as catalyst [10]. The corresponding optically active aldehydes were formed with excellent enantioselectivity of 94–98% ee in a wide range of solvents. With regard to yield, however, chloroform was found to be the solvent of choice, although yields were also good in acetonitrile and benzene. Under optimized reaction conditions (chloroform as solvent and reaction temperature +4 °C) the amount of catalyst was optimized. In the presence of 10 mol% proline 88% yield and 97% ee were obtained and the reaction time was very short, 20 min only. High efficiency was also observed when the amount of catalyst was reduced to 5 and 2 mol%. Enantioselectivity remained excellent, 97% ee, and yields were still high, but the reaction time was slightly prolonged, 45 min for 5 mol% and 2 h for 2 mol%; these conditions are still very attractive. The reaction is also highly enantioselective in the presence of only 0.5 mol% catalyst, although reaction time is significantly longer at 18 h (68% yield; 94% ee). An overview of optimization of catalytic loading is shown in Scheme 7.8.

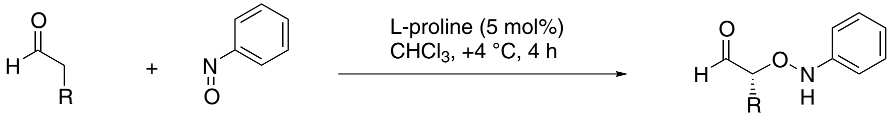
Investigation of the range of substrates showed this new proline-catalyzed α-aminooxylation route to be highly general [10]. The products were obtained in good to high yields and excellent enantioselectivity in the range 97–99% ee were obtained, irrespective of the pattern of substitution of the aldehydes [10]. An overview of the range of substrates under the optimized reaction conditions found by the MacMillan group is shown in Scheme 7.9. As examples, hexanal and 3-methylbutanal derived products, (*R*)-**11b** and (*R*)-**11c**, were obtained with yields of 79 and 85% and enantioselectivity of 98% ee and 99% ee, respectively. Because of the mild reaction conditions electron-rich π-systems also react efficiently, although these substrates are prone to oxidative degradation. Thus, aldehydes which contain olefinic and indolic functional groups were successfully converted into the desired products (*R*)-**11d** and (*R*)-**11f** with yields of 80 and 83% and high enantioselectivity of 99 and 98% ee, respectively. It should be added that the α-oxyaldehyde products were most conveniently isolated as the corresponding primary alcohols. Other



8a **10** **11a**

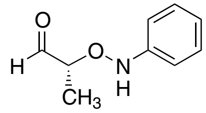
Entry	Catalytic amount [mol%]	Reaction time	Yield of 4a [%]	ee [%]
1	10	20 min	88	97
2	5	45 min	86	97
3	2	2 h	88	97
4	1	8 h	83	97
5	0.5	18 h	68	94

Scheme 7.8

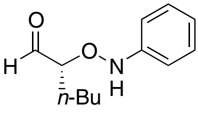


8 **10** **11**

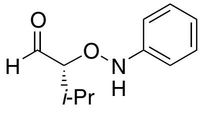
Selected examples



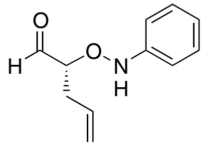
(*R*)-**11a**
88% yield
97% ee
(2 mol% of proline were used here)



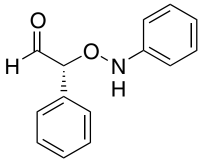
(*R*)-**11b**
79% yield
98% ee



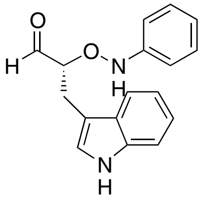
(*R*)-**11c**
85% yield
99% ee



(*R*)-**11d**
80% yield
99% ee
(10 mol% of proline were used here)

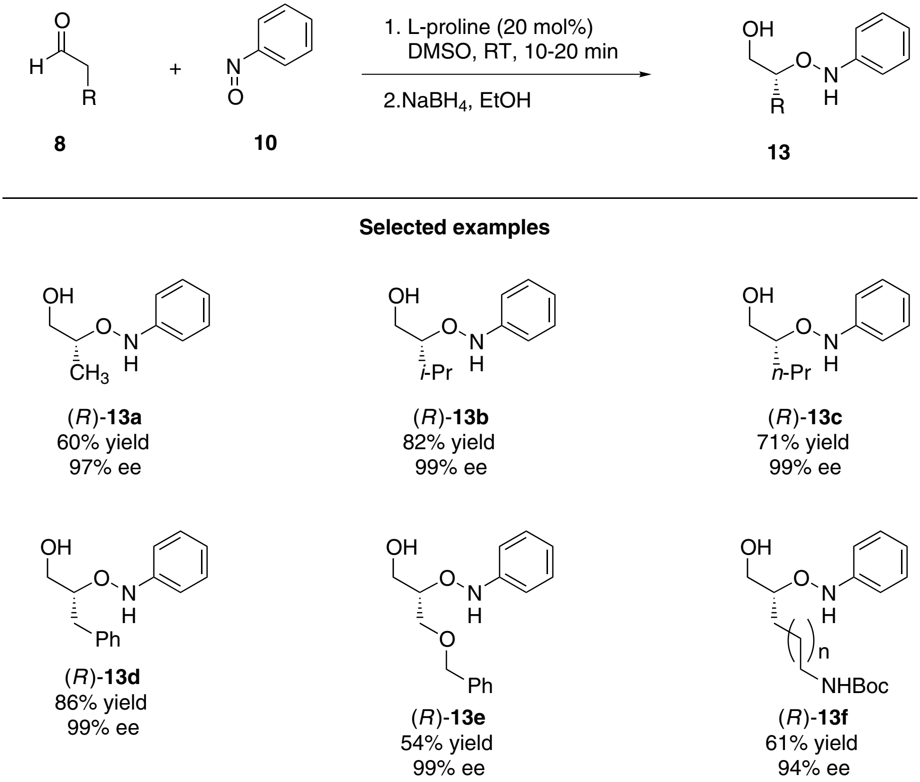


(*R*)-**11e**
60% yield
99% ee



(*R*)-**11f**
83% yield
98% ee

Scheme 7.9



Scheme 7.10

transformations, e.g. into a 1,2-amino alcohol, were also described by the MacMillan group [10].

In parallel, Zhong reported the α-aminooxylation of aldehydes, and *in-situ* derivatization into 1,2-diols, also using L-proline as catalyst [11]. α-Aminooxylation of isovaleraldehyde with nitrosobenzene at room temperature with 20 mol% catalyst was studied as model reaction. Because the oxyaldehyde product was found to be unstable during purification on silica gel, it was converted *in situ* into the 2-aminoxy alcohol (*R*)-**13b**. For this two-step, one-pot reaction a high yield (82%) of the product (*R*)-**13b** and excellent enantioselectivity of 99% ee was obtained (Scheme 7.10) [11]. Investigation of the substrate range showed the corresponding products **13** were obtained with excellent enantioselectivity in the range 94–99% ee. Selected examples are shown in Scheme 7.10.

Zhong rationalized the enantioselectivity by proposing an enamine mechanism which proceeds *via* the chair transition state shown in Figure 7.1 [11]. In this transition state, the *Si* face of an *E* enamine formed from the aldehyde and the catalyst L-proline approaches the less-hindered oxygen atom of nitrosobenzene leading to the chiral product with (*R*) configuration. This mechanism is in accordance with the proposed reaction mechanism for the aldol reaction (see chapter 6.2).

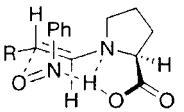
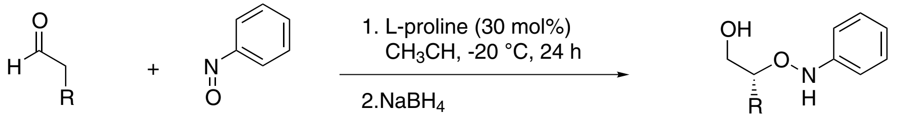


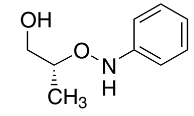
Fig. 7.1. Transition state proposed for the reaction. (From Ref. [11]).

The Hayashi group investigated the α-aminoxylation of propanal with nitrosobenzene in the presence of 30 mol% L-proline as model reaction [12a]. Because of the instability of the product, it was again converted directly into the corresponding α-aminoxy alcohol. Investigation of a variety of solvents revealed that acetonitrile was preferred, giving the desired product (*R*)-**13a** in quantitative yield and with excellent enantioselectivity (98% ee). Yields were lower at a reaction temperature of 0 °C than at −20 °C, because of the occurrence of side-reactions. Investigation of the range of substrates emphasized the high generality of this new, proline-catalyzed α-aminooxylation route [12a]. After reaction for 24 h the resulting products were formed in good to high yields, and excellent enantioselectivity in the range 95–99% ee was obtained irrespective of the pattern of substitution of the aldehyde [12a]. Selected examples are shown in Scheme 7.11. Both aliphatic and aromatic aldehydes were good substrates, affording, for example, products of types (*R*)-**13d** and (*R*)-**13g** in yields of 70% and 62%, respectively, and with high enantioselectivity – 99% ee for both reactions.

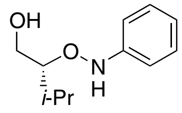


8 **10** **13**

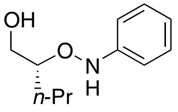
Selected examples



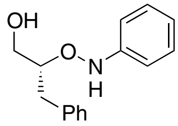
(*R*)-**13a**
quantitative yield
98% ee



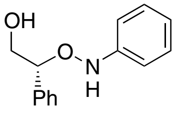
(*R*)-**13b**
77% yield
97% ee



(*R*)-**13c**
81% yield
95% ee

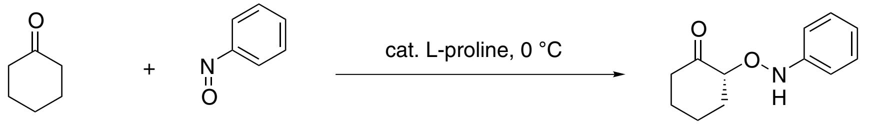


(*R*)-**13d**
70% yield
99% ee



(*R*)-**13g**
62% yield
99% ee

Scheme 7.11



9a

10

(*R*)-12a
79% yield
>99% ee

Scheme 7.12

The effect of the amount of catalyst (which is high, approximately 30 mol%) on this model reaction was also studied. Conducting the reaction with 10 mol% L-proline resulted in the same yield and enantioselectivity (quantitative yield for (*R*)-**13a**, and 98% ee; reaction time 24 h). A further decrease to 5 mol% led, however, to a slightly lower yield of 81%, although enantioselectivity was not affected (98% ee) [12a].

This α-aminooxylation has subsequently been successfully extended to the use of ketones as donors [12]. For example, use of cyclohexanone as donor led to (*R*)-**12a** in 79% yield and with an excellent enantioselectivity of >99% ee (Scheme 7.12) [12a]. Very recently, the Cordova group reported further examples of this proline-catalyzed α-aminooxylation [13]. In addition, this method has been successfully applied in the synthesis of corresponding chiral 1,2-diols after subsequent derivatization [13]. Furthermore, computational studies of transition states were carried out [13b].

In summary, the organocatalytic asymmetric α-aminooxylation of aldehydes and ketones with proline as catalyst is a highly enantioselective means of preparation of α-hydroxy carbonyl compounds, and their derivatives. Because this field has been developed only recently, more examples and work on extension of organocatalyst screening and process development can be expected in the near future.

References

1 For general reviews of α-amination of carbonyl compounds, see: (a) C. Greck, J. P. Genet, *Synlett* **1997**, 741–748; (b) J. P. Genet, C. Greck, D. Lavergne in: *Modern Amination Methods* (Ed.: A. Ricci), Wiley-VCH, Weinheim, **2000**, Chapter 3.

2 For selected examples of diastereoselective asymmetric syntheses using chiral enolates and N=N components as electrophiles, see: (a) C. Gennari, L. Colombo, G. Bertolini, *J. Am. Chem. Soc.* **1986**, *108*, 6394–6395; (b) D. A. Evans, T. C. Britton, R. L. Dorow, J. F. Dellaria, Jr., *J. Am. Chem. Soc.* **1986**, *108*, 6395–6397; (c) L. A. Trimble, J. C. Vederas, *J. Am. Chem. Soc.* **1986**, *108*, 6397–6399; (d) W. Oppolzer, R. Moretti, *Helv. Chim. Acta* **1986**, *69*, 1923–1926.

3 For "indirect" enantioselective catalytic syntheses using preformed enolsilanes and N=N components, see: (a) D. A. Evans, D. S. Johnson, *Org. Lett.* **1999**, *1*, 595–598; (b) Y. Yamashita, H. Ishitani, S. Kobayashi, *J. Can. Chem.* **2000**, *78*, 666–672.

4 For "direct" enantioselective catalytic syntheses using unmodified enolates, and N=N components, see: (a) D. A.

Evans, S. G. Nelson, *J. Am. Chem. Soc.* **1997**, *119*, 6452–6453; (b) K. Juhl, K. A. Jørgensen, *J. Am. Chem. Soc.* **2002**, *124*, 2420–2421.

5 N. Kumaragurubaran, K. Juhl, W. Zhuang, A. Bøgevig, K. A. Jørgensen, *J. Am. Chem. Soc.* **2002**, *124*, 6254–6266.

6 B. List, *J. Am. Chem. Soc.* **2002**, *124*, 5656–5657.

7 A. Bøgevig, K. Juhl, N. Kumaragurubaran, W. Zhuang, K. A. Jørgensen, *Angew. Chem.* **2002**, *144*, 1868–1871; *Angew. Chem. Int. Ed.* **2002**, *41*, 1790–1793.

8 R. O. Duthaler, *Angew. Chem.* **2003**, *115*, 1005–1008; *Angew. Chem. Int. Ed.* **2003**, *42*, 975–978.

9 (a) S. Bahmanyar, K. N. Houk, *J. Am. Chem. Soc.* **2001**, *123*, 12911–12912; (b) B. List, *Synlett* **2001**, 1675–1686.

10 S. P. Brown, M. P. Brochu, C. J. Sinz, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2003**, *125*, 10808–10809.

11 G. Zhong, *Angew. Chem.* **2003**, *115*, 4379–4382; *Angew. Chem. Int. Ed. Engl.* **2003**, *42*, 4247–4250.

12 (a) Y. Hayashi, J. Yamaguchi, K. Hibino, M. Shoji, *Tetrahedron Lett.* **2003**, *44*, 8293–8296; (b) Y. Hayashi, J. Yamaguchi, T. Sumiya, K. Hibino, M. Shoji, *J. Org. Chem.* **2004**, *69*, 5966–5973; (c) Y. Hayashi, J. Yamaguchi, T. Sumiya, M. Shoji, *Angew. Chem.* **2004**, *116*, 1132–1135; *Angew. Chem. Int. Ed.* **2004**, *43*, 1112–1115.

13 (a) A. Bøgevig, H. Sunden, A. Cordova, *Angew. Chem.* **2004**, *116*, 1129–1132; *Angew. Chem. Int. Ed.* **2004**, *43*, 1109–1112; (b) A. Cordova, H. Sunden, A. Bøgevig, M. Johansson, F. Himo, *Chem. Eur. J.* **2004**, *10*, 3673–3684.

14 For general reviews of synthesis of α-oxycarbonyl compounds *via* hydroxylation, see, for example, F. A. Davis, B. C. Chen in: *Houben–Weyl: Methods of Organic Chemistry* (Eds.: G. Helmchen, R. W. Mulzer, E. Schaumann), Georg Thieme Verlag, Stuttgart, **1995**, Vol. E21, pp. 4497 ff.

15 N. Momiyama, H. Yamamoto, *J. Am. Chem. Soc.* **2003**, *125*, 6038–6039.

8
Cycloaddition Reactions

8.1
[4+2]-Cycloadditions – Diels–Alder Reactions

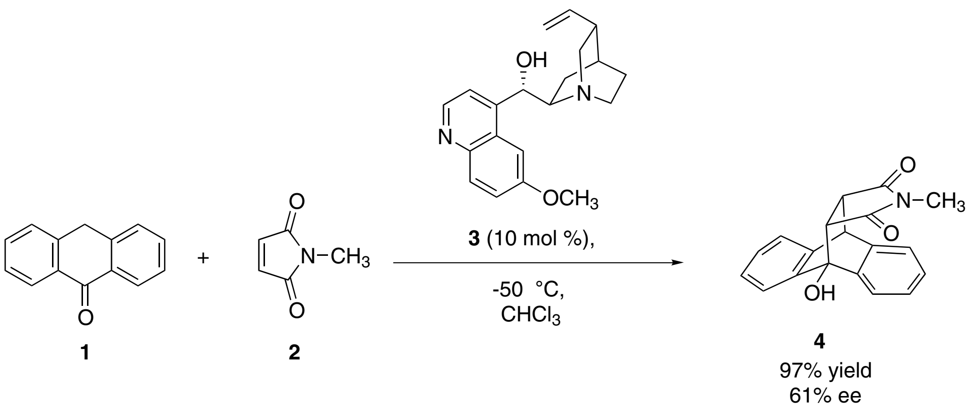
The asymmetric Diels–Alder reaction is one of the most important organic transformations and has proven to be a versatile means of synthesis of a large number of important chiral building blocks, e.g. intermediates in the total synthesis of natural products [1, 2]. Much work by many groups has emphasized that chiral metal complexes have a high potential for efficient asymmetric synthesis of "carbon skeletons" *via* a Diels–Alder reaction. The high state of the art of the asymmetric metal-catalyzed Diels–Alder reaction has also been shown by a recent excellent review [1]. For a long time it was not known that organocatalysts could be used to catalyze the Diels–Alder reaction and base-catalyzed Diels–Alder reactions, in particular, were regarded as "unusual" [3].

8.1.1
Diels–Alder Reactions Using Alkaloids as Organocatalysts

Kagan et al. reported the first organocatalytic asymmetric Diels–Alder reaction in 1989 [4]. Alkaloid bases, prolinol, and *N*-methylephedrine were investigated as organocatalysts. In the presence of 1–10 mol% of these chiral organocatalysts anthrone, **1**, reacts as a "masked diene" with *N*-methylated maleimide, **2**, forming Diels–Alder adducts **4** in high yields and with enantioselectivity up to 61% ee. Whereas yields are high – between 84 and 100% for all the organocatalysts tested – enantioselectivity varied substantially, depending on the type of catalyst. The best result was obtained with 10 mol% quinidine, **3**, in chloroform at −50 °C; the desired product **4** was obtained in 97% yield and with 61% ee (Scheme 8.1) [4]. Higher reaction temperatures led to reduced enantioselectivity. For example, enantioselectivity dropped from 61% ee to 35% ee when the reaction was performed at room temperature. During their study Kagan et al. also observed that the "free" hydroxyl group in the alkaloid organocatalyst was essential if high enantioselectivity was to be achieved.

A detailed study of the effect of several reaction conditions was also conducted by the Kagan group [3]. The nature of the solvent had a substantial effect on enantioselectivity. Compared with chloroform, much lower ee values were obtained with

Asymmetric Organocatalysis. Albrecht Berkessel and Harald Gröger
Copyright © 2005 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim
ISBN: 3-527-30517-3

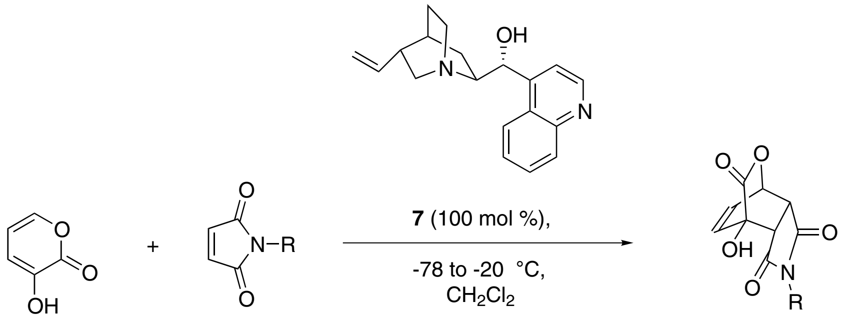


Scheme 8.1

THF, ethyl acetate, and methanol. In contrast, use of other chlorinated solvents, e.g. CCl_4, and cyclohexane resulted in higher enantioselectivity, comparable with that for chloroform. The range of dienophile substrates was also studied. Replacing *N*-methylmaleimide by *N*-phenylmaleimide, in the presence of quinidine as a catalyst, also led to a good yield, although enantioselectivity was lower (20% ee compared with 61% ee). Much slower reaction rates were observed when methyl acrylate and methyl fumarate were used and enantioselectivity was low (0% ee for methyl acrylate and 30% ee for methyl fumarate). With methyl maleate as a dienophile no reaction was observed. Mechanistic studies were also conducted by Kagan et al.; results were in accordance with a concerted [4+2]-cycloaddition process.

Extension of this method to the use of other diene components was demonstrated by Okamura et al. using 3-hydroxy-2-pyrone, **5**, as diene [5, 6]. When *N*-methylmaleimide, **2**, was used as dienophile initial screening of different types of amino alcohol as catalysts revealed that endo adducts were always formed as the major diastereomer [5]. Once again, cinchona alkaloids, particularly cinchonine and cinchonidine, were found to be the most promising catalysts. Under optimized reaction conditions this asymmetric Diels–Alder reaction afforded the endo adduct **8** in 98% yield and with 77% ee when chinchonidine was used as catalyst (Scheme 8.2) [5]. The diastereomeric ratio was d.r. (endo/exo) = 11:1. For this reaction, however, one equivalent of the catalyst was needed. Reducing the amount of catalyst to 10 mol% still gave the desired product **8** in high yield (100%) but with somewhat lower enantioselectivity (66% ee) and diastereoselectivity (d.r. (endo/exo) = 6.9:1) [5]. The opposite enantiomer was formed in 95% yield, and with 71% ee and a diastereomeric ratio of d.r. (endo/exo) = 7.1:1 in the presence of cinchonine as organocatalyst.

This asymmetric Diels–Alder reaction in the presence of cinchonidine (1 equiv.) also proceeds efficiently with *N*-benzylmaleimide, **6**, as dienophile, affording the product **9** in 99% yield, and with 54% ee (Scheme 8.2) [6]. The reaction is



5

2 ($R=CH_3$)
6 ($R=CH_2Ph$)

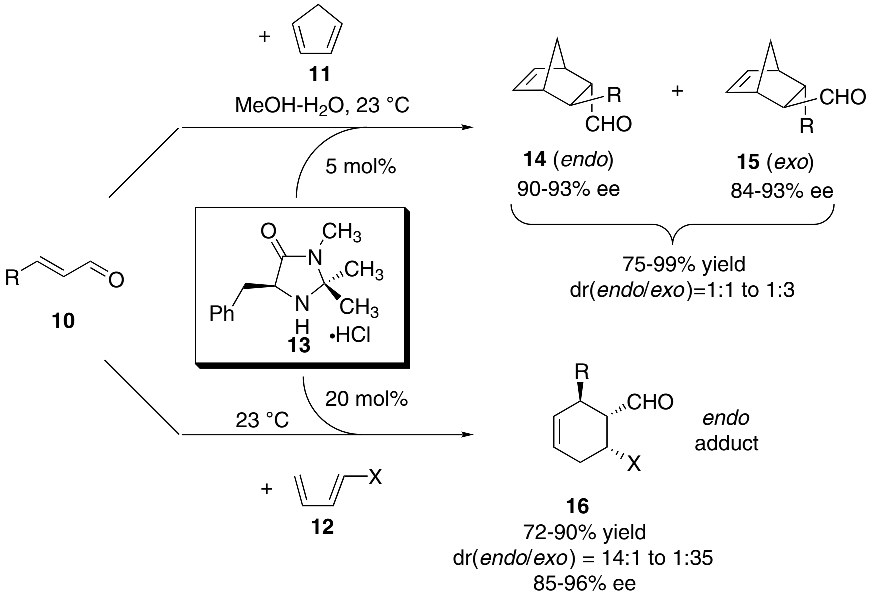
8 ($R=CH_3$): 98% yield
dr(*endo*/*exo*)=11:1
77% ee
9 ($R=CH_2Ph$): 99% yield
only *endo*-diasteromer
54% ee

Scheme 8.2

highly diastereoselective – formation of the exo diastereomer was not observed. In this conversion the use of quinine (1 equiv.) as catalyst led to improved enantioselectivity of 63% ee, and a still a high yield of 99%. If a smaller amount of catalyst was used slow addition of the diene was found to be beneficial. Thus, a yield of 95%, and nearly comparable enantioselectivity of 59% ee was achieved when the amount of catalyst was 30 mol%. The product **9**, a key intermediate in the synthesis of an SP antagonist, can be readily obtained as the enantiomerically pure compound by simple recrystallization.

8.1.2
Diels–Alder and hetero-Diels-Alder Reactions Using α-Amino Acid Derivatives as Organocatalysts

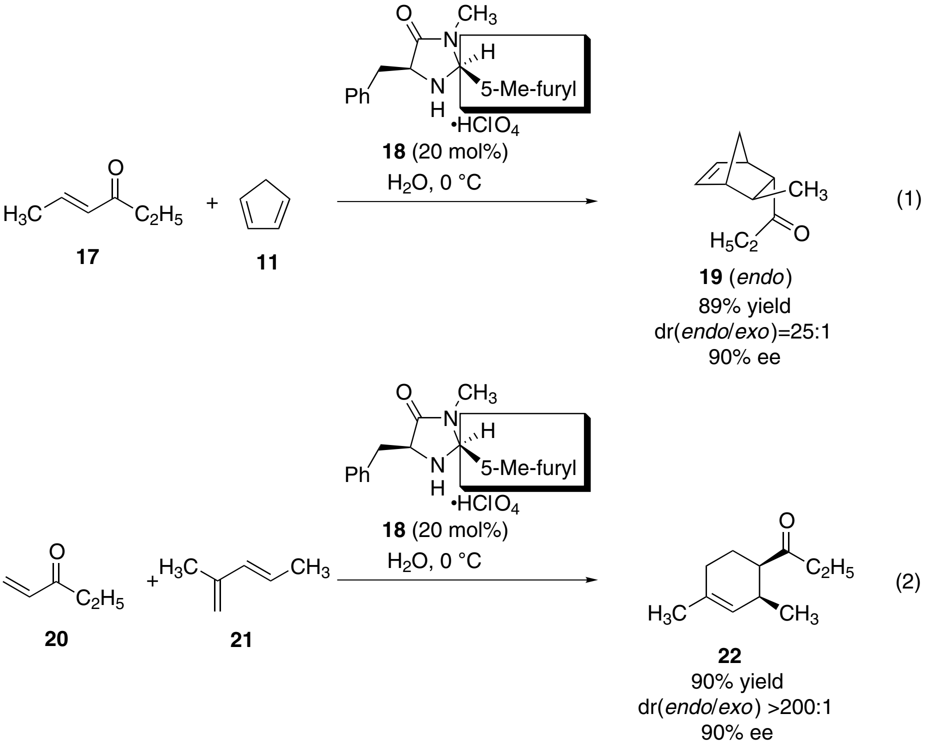
The first highly enantioselective and general asymmetric organocatalytic Diels–Alder reaction was developed very recently by the MacMillan group, who used HCl salts of α-amino acid-derived imidazolidinones (of type **13**) as catalysts [7, 8]. The catalytic activity of these chiral amino acid derivatives, e.g. **13**, which was identified as the optimum catalyst, is based on their capacity to reversibly form iminium ions with the α,β-unsaturated aldehydes, **10**. Other α-amino acid derivatives have also been investigated as catalysts, but led to lower yields and enantioselectivity. The organocatalytic Diels–Alder reaction in the presence of **13** proceeds with high diastereoselectivity (exo/endo ratio up to 35:1) and with up to 96% ee (Scheme 8.3) when using non-cyclic dienes of type **12** [7]. Use of cyclopentadiene **11** led to good to high yields of 75–99% and diastereoselectivity in the range d.r. = 1:1 to 3:1; this enabled isolation of both endo and exo adducts, **14** and **15**. Interestingly, enantioselectivity was high (ee values up to 93%) for both adducts.



Scheme 8.3

It is worthy of note that a broad range of dienophiles and dienes can be used without loss of yield or enantioselectivity. Thus, dienophile components of type **10** bearing aromatic and alkyl substituents are tolerated. This organocatalytic Diels–Alder reaction is, furthermore, general with regard to diene structure, as has been demonstrated by the use of cyclopentadiene, **11**, and non-cyclic dienes of type **12** (Scheme 8.3). Although yield and enantioselectivity were almost always high, diastereoselectivity varied from d.r. = 1:1 to 35:1. This efficient organocatalytic Diels–Alder reaction was performed under an aerobic atmosphere and in the presence of "non-dried" solvents.

This organocatalytic concept based on iminium activation was successfully extended by MacMillan et al. to the first enantioselective catalytic Diels–Alder reaction with simple ketone dienophiles [8]; previously, low enantiocontrol had usually been observed for this type of substrate. Whereas the previously developed organocatalyst **13** gave less satisfactory results, the analogous amino acid derivative bearing two stereogenic centers, **18**, was found to be highly efficient for this type of reaction. For example, the Diels–Alder product **19** was obtained in 89% yield, with 90% ee, and impressive diastereoselectivity of d.r. (endo/exo) = 25:1 (Scheme 8.4, Eq. 1). The reaction proceeded well with a broad range of substituted non-cyclic and cyclic enones giving the desired products in yields of up to 89%, diastereoselectivity up to d.r. (endo/exo) = 25:1, and enantioselectivity of up to 92% ee [8]. The generality of the Diels–Alder reaction using enones was also shown for the diene component. When acyclic dienes, e.g. **21**, were used as diene component, instead of cyclopentadiene, excellent diastereoselectivity of up to d.r. (endo/exo) >

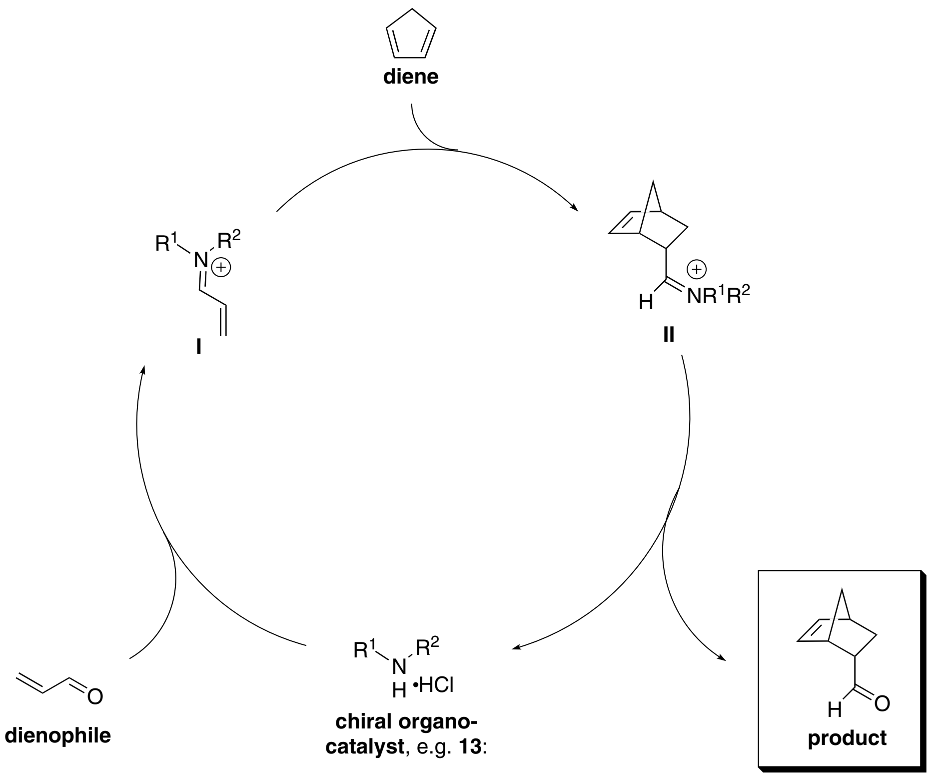


Scheme 8.4

200 accompanied by high yields and enantioselectivity of up to 98% ee were obtained [8]. A representative example is shown in Scheme 8.4, Eq. (2).

The principle of the reaction mechanism is summarized in Scheme 8.5. A key step is the reversible formation of the iminium ion **I** starting from the imidazolidinone-type organocatalyst and the α,β-unsaturated carbonyl component [7]. This LUMO-lowering activation of the dienophile *via* iminium ion formation is followed by subsequent Diels–Alder cycloaddition with the diene and formation of the iminium ion **II**. These steps proceed with high enantiocontrol. Molecular modeling calculations also have shown that stereocontrolled synthesis of the iminium ion is a prerequisite for achieving high enantioselectivity, because the (*E*) and (*Z*) iminium ion isomers are expected to undergo cyclization from opposite enantiofaces [7].

The preparation of immobilized catalysts related to the imidazolidinone-type organocatalyst **13** and their application in the asymmetric Diels–Alder reaction was reported by Pihko and co-workers [9]. The reactivity of the immobilized catalysts depended on the type of solid support. The silica-supported imidazolidinone **24**, which was prepared starting from *N*-Fmoc-protected L-phenylalanine, was found to be a highly active organocatalyst. Several dienes and α,β-unsaturated aldehydes have been successfully used in the presence of only 3.3 to 20 mol% **24**, usually

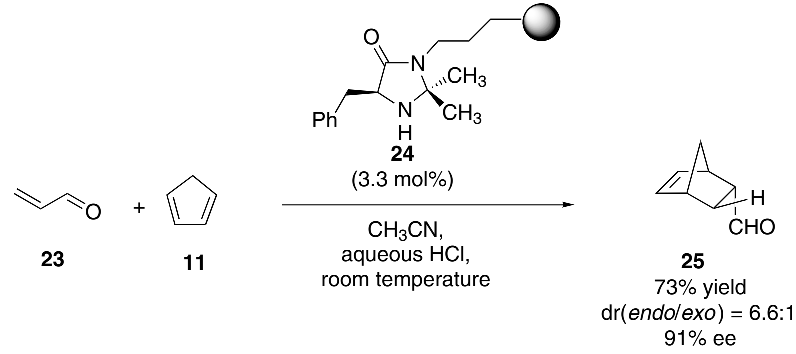


Scheme 8.5

with good yields (up to 83%) and high enantioselectivity (up to 91% ee). endo/exo Diastereoselectivity varied from d.r. (endo/exo) = 1.1:1 to 14.1. A representative example is shown in Scheme 8.6. Results obtained by use of solid-supported catalysts were usually equal or superior to those obtained with the analogous "free" solution-phase catalyst, **13**. The solid-supported catalysts can be easily recovered by filtration, and re-using the recovered catalysts gives similar results. In addition, recently a chiral pyrrolidine derivative has been used as an efficient organocatalyst for the hetero-Diels–Alder reaction by the Jørgensen group, achieving high enantioselectivities of up to 94% ee [10].

8.1.3
Diels–Alder and hetero-Diels–Alder Reactions Using C_2-symmetric Organocatalysts

Chiral amidinium organocatalysts also have been shown to be suitable catalysts for the Diels–Alder reaction, and have been applied in the formation of the skeleton of estrone and norgestrel [11]. The Göbel group first designed suitable axially chiral mono-amidinium ions for this reaction (Scheme 8.7, Eq. 1); the type **27** product was obtained highly enantioselectively [11a,b]. A drawback of these organocatalysts, however, is the length of the synthetic route required to prepare them. Very



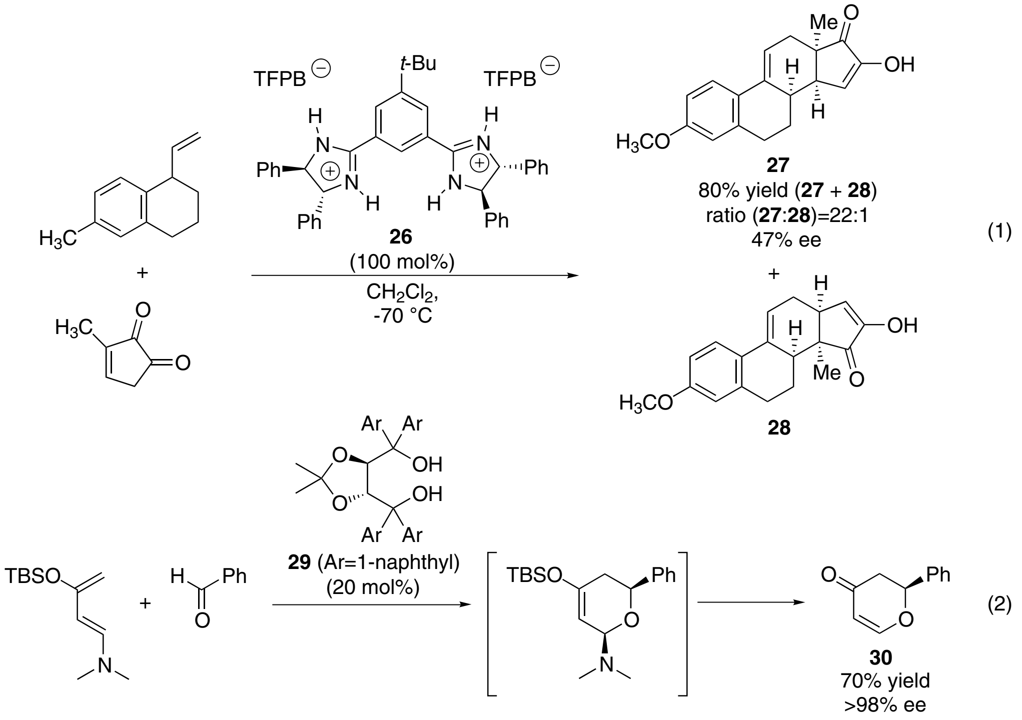
Scheme 8.6

recently, Göbel and Tsogoeva et al. designed an C_2-symmetric bis-amidinium salt **26** which is more accessible, because this organocatalyst can be synthesized by a short synthetic route [11c]. In the presence of bis-amidinium catalyst **26**, the product **27** was formed with enantioselectivity up to 47% ee. A representative example is shown in Scheme 8.7, Eq. 1 [11c]. The rate of reaction with the C_2-symmetric bis-amidinium salts is much higher than that with the mono-amidinium salts. Substitution of the phenyl group in the catalyst structure by bulkier groups is regarded as a strategy for further optimization of the catalyst. The Rawal group reported a highly efficient asymmetric hetero-Diels–Alder reaction using 20 mol% of TADDOL ($\alpha,\alpha,\alpha',\alpha'$,tetraaryl-1,3-dioxolan-4,5-dimethanol) **29** as an organocatalyst [12]. After hetero-Diels–Alder reaction and subsequent derivatization, the desired final products of type **30** were obtained in yields of 52–97%, and with enantioselectivities of 92 to >98% ee. A selected example is shown in Scheme 8.7, Eq. 2. This reaction has been successfully carried out with a range of aldehydes. Notably, the monomethyl and dimethylether derivatives of **29** were poor catalysts, indicating that the hydrogen bonding capability of **29** is a prerequisite for the catalytic function [12].

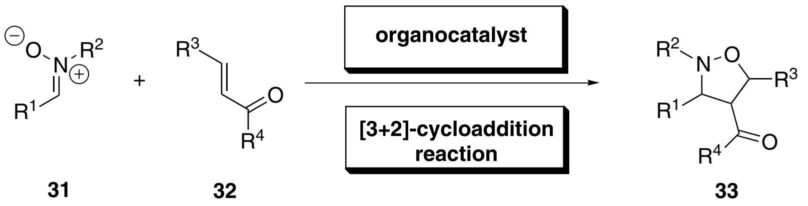
In conclusion, the organocatalytic asymmetric Diels–Alder reaction is a highly efficient process, in particular when using TADDOL **29**, as shown by the Rawal group, as well as the imidazolidinone-type catalysts, e.g. **13** and **18**, developed by the MacMillan group. In this connection a specific highlight is certainly the application of this concept in the first highly enantioselective catalytic Diels–Alder reaction with α,β-unsaturated ketones as dienophiles. Furthermore, suitable organocatalyst have been found for the hetero-Diels–Alder reaction as demonstrated by the Jørgensen group.

8.2
[3+2]-Cycloadditions: Nitrone- and Electron-deficient Olefin-based Reactions

In addition to [4+2]-cycloadditions, the asymmetric [3+2]-cycloaddition reaction of a nitrone, **31**, with an α,β-unsaturated carbonyl compound, **32**, is of wide interest [13]. The resulting isoxazolidine products of type **33** are intermediates in the prep-



Scheme 8.7



Scheme 8.8

aration of a wide range of biologically important compounds, e.g. β-lactams and non-natural amino acids [13, 14]. The concept of this [3+2]-cycloaddition – with regard to organocatalytic application – is shown schematically in Scheme 8.8.

Several asymmetric versions of cycloaddition reactions with nitrones in the presence of optically active metal complexes as Lewis-acid catalysts have been reported [15]. Because of a lack of suitable chiral catalysts, however, the asymmetric design of this reaction was found to be difficult when using α,β-unsaturated aldehydes as substrates, because these compounds are poor substrates for metal catalysts, probably because of preferential coordination of the Lewis acid catalyst to the nitrone in the presence of monodentate carbonyl compounds. Consequently, inhibition of the catalyst occurs.

A solution addressing this synthetic issue is an extension of the recently devel-

oped organocatalytic Diels–Alder reaction reported by the MacMillan group. This concept has now been successfully applied to [3+2]-cycloadditions with nitrones [16, 17]. This transformation is also the first example of an organocatalytic 1,3-dipolar cycloaddition. Conversion of *N*-benzylidene benzylamine *N*-oxide, **31a**, with (*E*)-crotonaldehyde, **32a**, to the isoxazolidine product **35a** was investigated as an initial model reaction. Detailed catalyst screening revealed that, in accordance with the Diels–Alder reaction, the phenylalanine-derived imidazolidinone acid salt **34**·HCl was the preferred organocatalyst. Study of different types of Brønsted acid component showed that **34**·$HClO_4$ was most effective. The scope of the organocatalytic [3+2]-cycloaddition of nitrones, e.g., **31a–g**, to α,β-unsaturated aldehydes **32a–b** was investigated using this catalyst. Selected examples are shown in Scheme 8.9.

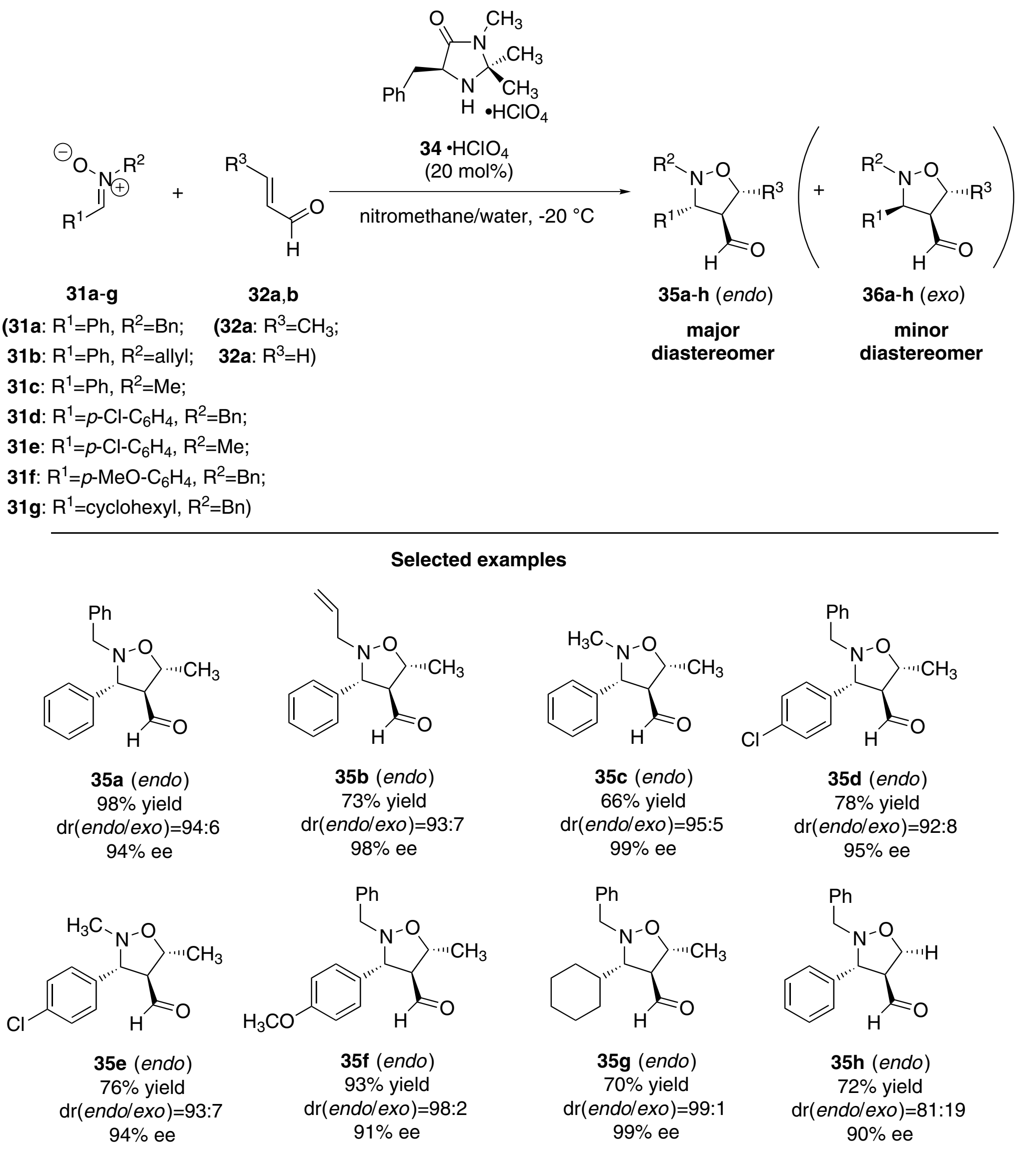
The resulting isoxazolidines *endo*-**35** were obtained in yields of up to 98%, with diastereomeric ratios of d.r. (endo/exo) of 80:20 to 99:1, and with enantioselectivity of 90–99% ee. The endo product was always formed as preferred diastereomer.

This 1,3-dipolar cycloaddition not only gave excellent results but was also found to be very general with regard to the nitrone component. Several types of aryl- and alkyl-substituted nitrone have been applied successfully. Irrespective of the substitution pattern, high diastereomeric ratios and enantioselectivity were obtained (see Scheme 8.9, products **35a**,**d**,**f**,**g**). Variation of the *N*-alkyl group is also possible. As can be see from Scheme 8.9 (see, e.g., products **35a–c**), the reactions also proceed well when an *N*-allyl and *N*-methyl-substituted nitrone is used. Acrolein, **32b**, and crotonaldehyde, **32a**, were used as the aldehyde component. It is noteworthy that this reaction is also suitable for use on a larger scale, as has been demonstrated by the 25 mmol-scale preparation of *endo*-**35a** (98% yield, 94% ee) starting from nitrone **31a** and crotonaldehyde.

The reactions can be performed under an aerobic atmosphere using wet solvents, which makes this procedure even more attractive. Another advantage is the easy access to the catalyst, which is based on the inexpensive amino acid phenylalanine.

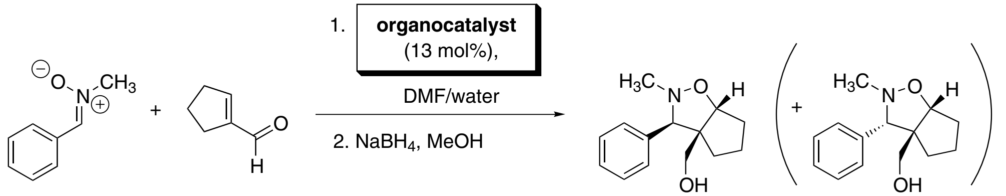
A detailed investigation of the potential of this organocatalytic [3+2]-cycloaddition for application to cyclic α,β-unsaturated aldehydes was conducted by the Karlsson group [18]. A broad range of organocatalyst comprising a MacMillan-type imidazolidine salt, **34**·HCl, and pyrrolidine derivatives, e.g. **41**·2HCl, were used. The [3+2]-cycloaddition of nitrone **31c** with cyclopent-1-ene carboxaldehyde was chosen as model reaction. In this reaction the imidazolidine salt **34**·HCl led to the desired product in low yield (19%) and enantioselectivity (5% ee) only after 144 h. When azabicyclo[3.3.0]octane-derived salts, e.g. **40**, were used the desired isoxazolidine cycloadduct **38** was obtained in yields up to 61% and with enantioselectivity up to 76% ee. Diastereoselectivity obtained with this type of catalyst was in the range d.r. = 72:28 to 89:11. A selected example is shown in Scheme 8.10.

Diastereoselectivity and enantioselectivity were observed to increase substantially when proline-derived diamine salts were used as organocatalysts. In particular, the pyrrolidinium salt **41**·2HCl was found to be very useful, furnishing the target molecule **38** in 70% yield with diastereoselectivity of d.r. = 95:5 and enantioselec-

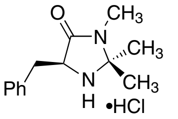
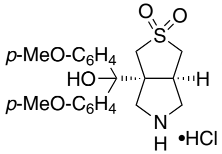
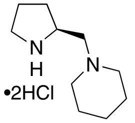


Scheme 8.9

tivity of 91% ee (reaction time 144 h; Scheme 8.10). The amount of catalyst was 13 mol% for all the catalysts tested. The reaction also proceeds in the presence of smaller amounts of catalyst, although the rate of reaction is low. Use of only 1 mol% **41**·2HCl led to the formation of the cycloadduct **38** with d.r. = 97:3 and 91% ee. The yield, however, was 21% only after 120 h. It should be noted that proline-derived amino alcohols or their *O*-methylated derivatives were not suitable catalysts.



31c 37 38 major diastereomer 39 minor diastereomer

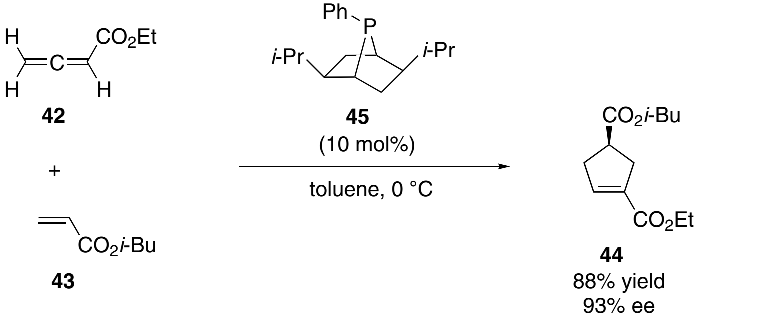
Organocatalyst		Yield [%]	d.r.	ee [%]
	34•HCl	19	86:14	-5
	40•HCl	61	80:20	70
	41•2HCl	70	95:5	91

Scheme 8.10

Another type of asymmetric [3+2]-cycloaddition catalyzed by organocatalysts is the cycloaddition of 2,3-butadienoates and electron-deficient olefins [19]. Such an approach has been reported by the Zhang group using novel phosphabicyclo[2.2.1]heptanes as catalysts. This new type of phosphine with a rigid phosphabicyclic structure gave better results than were obtained with several known chiral phosphines. For example, in the presence of 10 mol% phosphine **45** the [3+2]-cycloaddition of 2,3-butadienoate **42** and acrylate **43** gives one regioisomer only, **44** (Scheme 8.11); yield (88%) and enantioselectivity (93% ee) are both high.

A study of the range of substrates revealed regioselectivity was usually high, in the range 94:6 to 100:0. This [3+2]-cycloaddition developed by the Zhang group is a powerful method for asymmetric synthesis of optically active cyclopentene products. A reaction mechanism has also been proposed. The initial step is formation of an adduct between the phosphine catalyst and the 2,3-butadienoate, followed by cycloaddition with the acrylate component as a key step.

In conclusion, new types of [3+2]-cycloaddition have been developed which are based on use of organocatalysts. The [3+2]-cycloaddition of nitrones and



Scheme 8.11

α,β-unsaturated carbonyl compounds proceeds very efficiently, particularly if chiral imidazolidine and pyrrolidine salts are used as catalysts. The [3+2]-cycloadditions proceed with high diastereo- and enantioselectivity, and are an attractive route for preparation of enantiomerically pure isoxazolidines. Furthermore, [3+2]-cycloaddition of 2,3-butadienoates with electron-deficient olefins is catalyzed with high enantioselectivity by chiral phosphines with a rigid phosphabicyclic structure.

References

1 For an excellent review of asymmetric Diels–Alder reactions, see: E. J. Corey, *Angew. Chem.* **2002**, *114*, 1724–1741; *Angew. Chem. Int. Ed.* **2002**, *41*, 1650–1667.

2 For the original work on the Diels–Alder reaction, see: O. Diels, K. Alder, *Justus Liebigs Ann. Chem.* **1926**, *450*, 237–254; O. Diels, K. Alder, *Justus Liebigs Ann. Chem.* **1927**, *460*, 98–122.

3 O. Riant, H. B. Kagan, L. Ricard, *Tetrahedron* **1994**, *50*, 4543–4554.

4 O. Riant, H. B. Kagan, *Tetrahedron Lett.* **1989**, *30*, 7403–7406.

5 H. Okamura, Y. Nakamura, T. Iwagawa, M. Nakatani, *Chem. Lett.* **1996**, 193–194.

6 H. Okamura, H. Shimizu, Y. Nakamura, T. Iwagawa, M. Nakatani, *Tetrahedron Lett.* **2000**, *41*, 4147–4150.

7 K. A. Ahrendt, C. J. Borths, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2000**, *122*, 4243–4244.

8 A. B. Northrup, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2002**, *124*, 2458–2460.

9 S. S. Selkälä, J. Tois, P. M. Pihko, A. M. P. Koskinen, *Adv. Synth. Catal.* **2002**, *344*, 941–945.

10 K. Juhl, K. A. Jørgensen, *Angew. Chem.* **2003**, *115*, 1536–1539; *Angew. Chem. Int. Ed.* **2003**, *42*, 1498–1501.

11 (a) T. Schuster, M. Kurz, M. W. Göbel, *J. Org. Chem.* **2000**, *65*, 1697–1701; (b) T. Schuster, M. Bauch, G. Dürner, M. W. Göbel, *Org. Lett.* **2000**, *2*, 179–181; (c) S. B. Tsogoeva, G. Dürner, M. Bolte, M. W. Göbel, *Eur. J. Org. Chem.* **2003**, 1661–1664.

12 Y. Huang, A. K. Unni, A. N. Tadani, V. H. Rawal, *Nature* **2003**, *424*, 140.

13 For a review of [3+2]-cycloaddition reactions, see: K. V. Gothelf, K. A. Jorgensen, *Chem. Rev.* **1998**, *98*, 863–910.

14 For example, see: M. Frederickson, *Tetrahedron* **1997**, 53, 403–425.

15 For selected contributions to the field

of enantioselective metal-catalyzed cycloadditions with nitrones, see: (a) D. Keirs, D. Moffat, K. Overton, R. Tomanek, *J. Chem. Soc., Perkin Trans 1* **1991**, 1041–1051; (b) K. B. Jensen, M. Roberson, K. A. Jørgensen, *J. Org. Chem.* **2000**, *65*, 9080–9084; (c) S. Iwasa, S. Tsushima, T. Shimada, H. Nishiyama, Tetrahedron Lett. **2001**, *42*, 6715–6717; (d) X. Ding, K. Taniguchi, Z. Ukata, K. Inomata, *Chem. Lett.* **2001**, 468–469; (e) S. Iwasa, S. Tsushima, T. Shimada, H. Nishiyama, *Tetrahedron* **2002**, *58*, 227–232; (f) S. Murahashi, Y. Imada, T. Kawakami, K. Harada, Y. Yonemushi, N. Tomita, *J. Am. Chem. Soc.* **2002**, *124*, 2888–2889; (g) F. Viton, G. Bernardinelli, E. P. Kündig, *J. Am. Chem. Soc.* **2002**, *124*, 4968–4969.

16 W. S. Jen, J. J. M. Wiener, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2000**, *122*, 9874–9875.

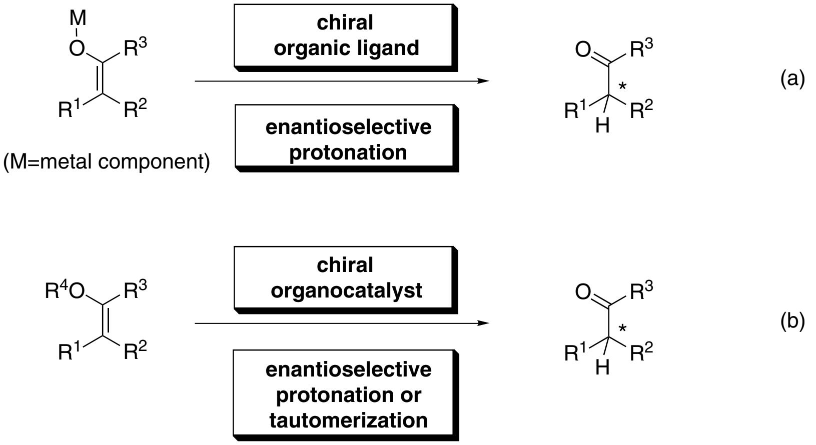
17 D. W. C. MacMillan, PCT Int. Appl. WO 2003002491, **2003**.

18 S. Karlsson, H.-E. Hogberg, *Tetrahedron: Asymmetry* **2002**, *13*, 923–936.

19 G. Zhu, Z. Chen, Q. Jiang, D. Xiao, P. Cao, X. Zhang, *J. Am. Chem. Soc.* **1997**, *119*, 3836–3837.

9
Protonation of Enolates and Tautomerization of Enols

Enantioselective protonation reactions are an important tool for synthesis of carbonyl compounds with a stereogenic carbon center in the α-position [1–4]. These compounds are useful building blocks as intermediates for, e.g., pharmaceuticals and fragrance compounds. For the latter, the industrial relevance of these reactions has already been demonstrated [3]. Most protonations are still based on the use of stoichiometric amounts of chiral auxiliary, although catalytic versions are gaining increasing importance. Metal enolates as indicated in Scheme 9.1, Eq. (a) or metal-free analogs as indicated in Scheme 9.1, Eq. (b) have been used as achiral precursors. When metal enolates are used a transition state is formed consisting of the chiral organic molecule and the metal. Thus, although this reaction starts with an organic molecule as "catalyst" it can be regarded as a transition metal complex-catalyzed synthesis in which the metal, surrounded by the chiral organic molecule as chiral ligand, plays an important role in the asymmetric induction process. Because this type of process seems to be more a metal complex-catalyzed reaction than a "pure" organocatalytic reaction, and taking into account that the subject of enantioselective protonation has already been reviewed extensively



Scheme 9.1

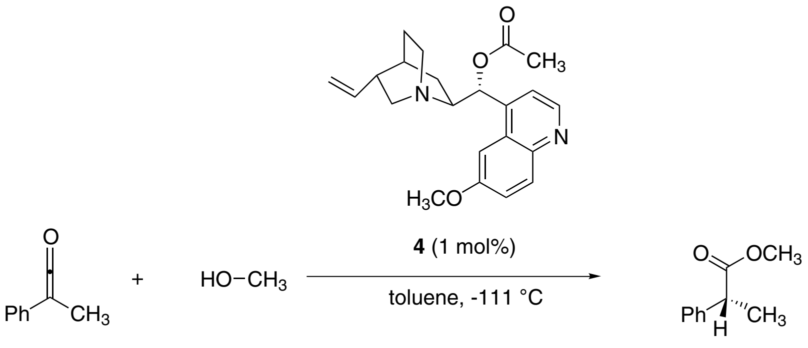
Asymmetric Organocatalysis. Albrecht Berkessel and Harald Gröger
Copyright © 2005 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim
ISBN: 3-527-30517-3

[1–4], this type of reaction, which is very efficient and often highly enantioselective, will be not discussed below.

The following discussion will cover representative examples of protonations proceeding in the absence of metal components, as in Scheme 9.1, Eq. (b), or related variations.

9.1
Enantioselective Protonation of Enolates formed *in situ* from Enolate Precursors

Enantioselective protonation can be achieved by organocatalysis starting from ketenes [5–7]. This approach was described by Pracejus and co-workers as early as the 1960s and is thus one of the earliest contributions in the field of asymmetric organocatalysis. The most successful reaction in terms of enantioselectivity is shown in Scheme 9.2. In the presence of only 1 mol% *O*-acetylquinine, **4**, the carboxylate (*R*)-**3** is obtained with 74% ee when the reaction is conducted at −111 °C [5]. Phenylmethylketene was chosen as starting material, because of the relatively good availability, stability, and the presence of two sterically different substituents. The initial step is nucleophilic addition of a 1:1 aggregate of the alcohol and the chiral tertiary amine organocatalyst to the ketene, forming a postulated ammonium enolate salt. Subsequent enantioselective proton-transfer from the ammonium ion to the enolate furnishes the carboxylate product (*R*)-**3**. A prerequisite for an enantioselective reaction is the very low temperature of −110 °C [5] – performing the reaction at −70 °C instead of −110 °C led to an almost racemic ester (< 5% ee instead of 74% ee). Use of brucine and acetylchinidine led to the opposite, (*S*), ester as the major enantiomer, but enantioselectivity was below 40% ee [5]. It should be added that this reaction is very complex, because of the presence of a variety of rapidly interconverting conformers and, thus, competing tran-



1 **2** (*R*)-**3**
74% ee

Scheme 9.2

sition states [1]. Asymmetric nucleophilic addition to prochiral ketenes ultimately relying on asymmetric enolate protonation are also discussed – in particular with respect to the recent developments – in chapter 13.2.

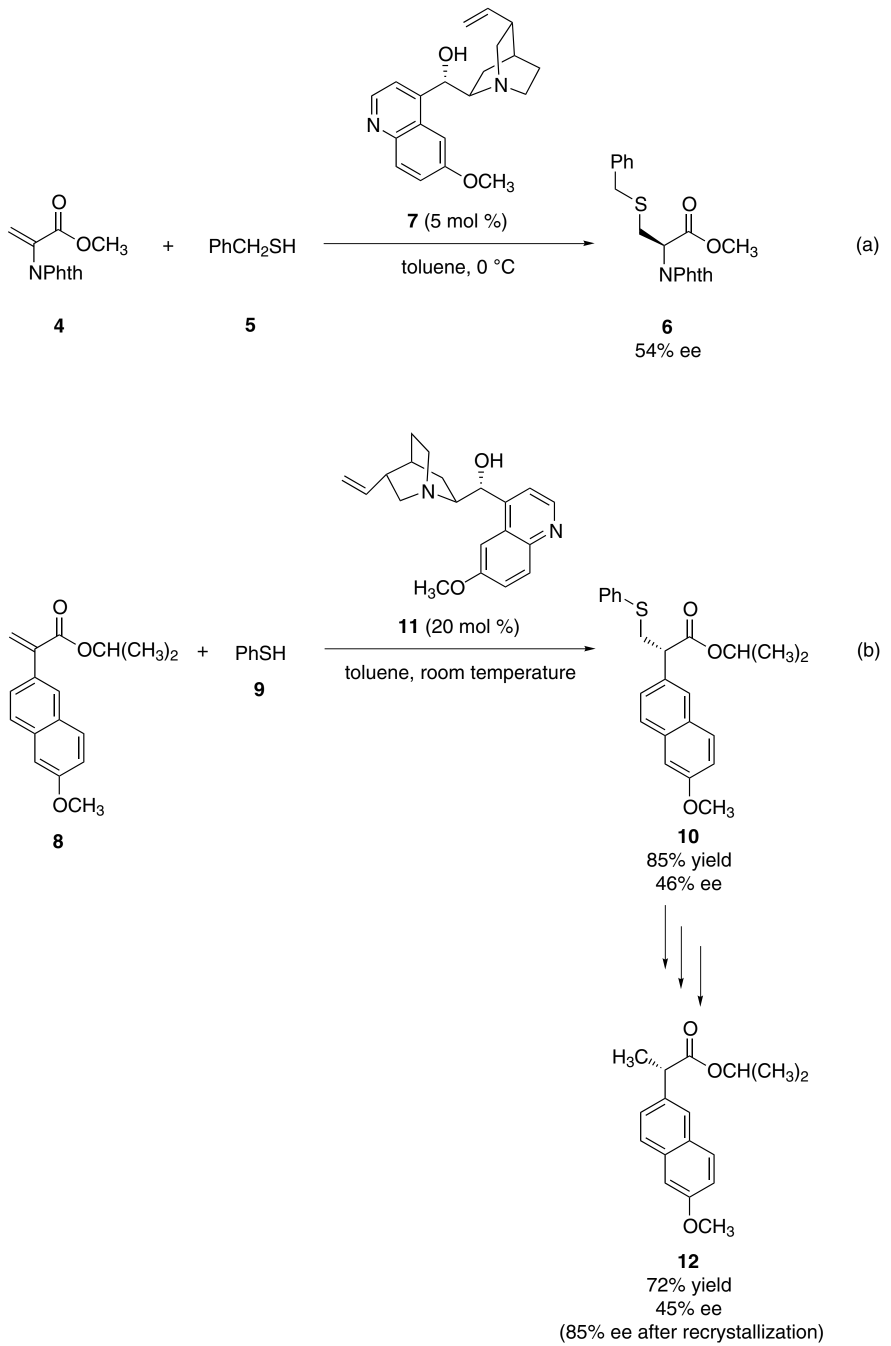
Pracejus and co-workers also described an alternative method for preparing suitable enolates *in situ*, Michael addition of a thiol to an acrylate [8]. A selected example of this reaction, for which enantioselectivity is in the range 20–54% ee, is shown in Scheme 9.3, Eq. (a). Use of a catalytic amount (5 mol%) of quinidine, **7**, gave the (*R*)-cysteine derivative **6** with 54% ee. Benzyl thiol, benzhydryl thiol, or triphenylmethyl thiol were used as the thiol component. In addition to acrylates, nitroalkenes were used as a starting material.

Related enantioselective protonation reactions based on the use of thiophenol as a nucleophile have also been reported by Kumar et al.; these reactions led to enantioselectivity of 45–51% ee [9]. For example in the presence of 20 mol% quinine **11** the adduct **10** was synthesized in 85% yield and with 46% ee (Scheme 9.3, Eq. b). Reaction product **10** has subsequently been used as an intermediate in the synthesis of (*S*)-naproxen, **12**, which was obtained in 85% ee (after recrystallization).

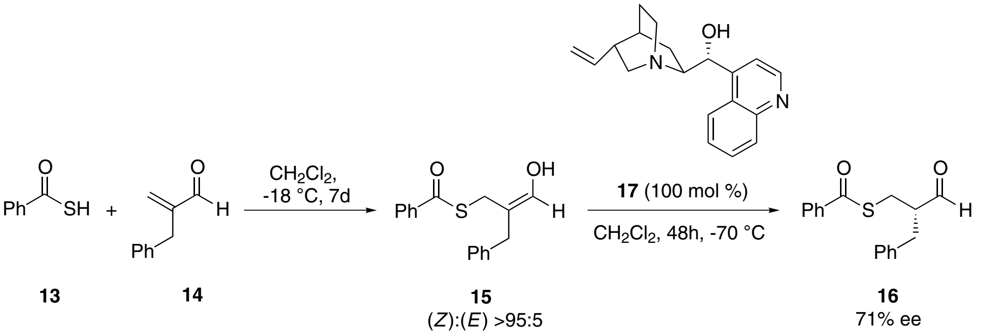
9.2
Enantioselective Tautomerization of Enols Generated *in situ*

The Duhamel group has developed an efficient method for protonation involving use of a metastable enol (Scheme 9.4) [10]. This metastable enol, which is geometrically pure with a (*Z*):(*E*) ratio of >95:5, was prepared by addition of thiobenzoic acid **13** to the enal **14**. Tautomerization reactions were subsequently conducted in the presence of chiral amino alcohols as organocatalysts to give the desired products with enantioselectivity of 58 and 71% ee when using *N*-methylephedrine and cinchonidine, respectively, as organocatalysts. Use of 100 mol% of cinchonidine, **17**, as organocatalyst furnished the product **16** with 71% ee when the reaction was performed at −70 °C in dichloromethane for 48 h [10].

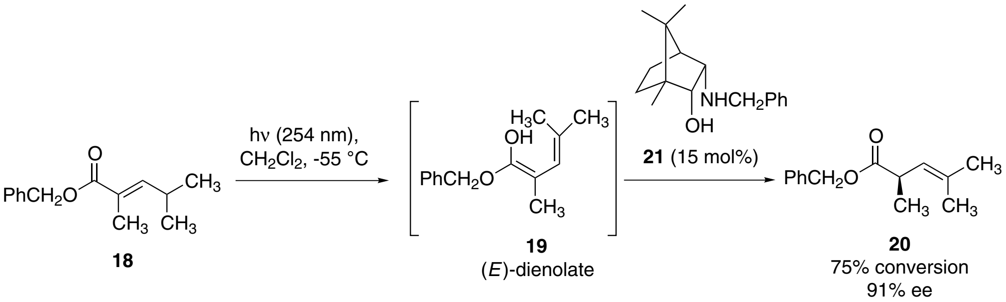
The photochemical *in-situ*-generation of dienols and their subsequent enantioselective organocatalytic tautomerization reactions in the presence of chiral β-amino alcohols was reported by Pete and co-workers [11–18]. For these photodeconjugation reactions, α,β-unsaturated esters and lactones serve as starting materials. The course of the reaction in the presence of a β-amino alcohol as organocatalyst is shown in Scheme 9.5. The initial photochemical formation of the transient dienol **19**, which involves intramolecular γ-hydrogen bond abstraction of the allylic hydrogen and subsequent tautomerization in the presence of 10–15 mol% chiral β-amino alcohol organocatalyst, gives the desired chiral carboxylates of type **20** bearing a stereogenic center in α-position, with enantioselectivity up to 91% ee [17]. An example is shown in Scheme 9.5. Prerequisites for efficient reaction are rigorous exclusion of moisture, use of an apolar solvent, and a low reaction temperature of approximately −55 °C [16–18]. In the presence of moisture and protic or basic solvents racemates are formed, because water and these types of solvent seem to compete with the chiral organocatalyst during the proton transfer step [16].


OH
N
N
OCH3
7 (5 mol %)
toluene, 0 °C
O
OCH3
NPhth
+
PhCH2SH
4
5
Ph
S
O
OCH3
NPhth
6
54% ee
(a)
OH
N
N
H3CO
11 (20 mol %)
toluene, room temperature
O
OCH(CH3)2
+
PhSH
9
OCH3
8
Ph
S
O
OCH(CH3)2
OCH3
10
85% yield
46% ee
(b)
O
H3C
OCH(CH3)2
OCH3
12
72% yield
45% ee
(85% ee after recrystallization)

Scheme 9.3



Scheme 9.4



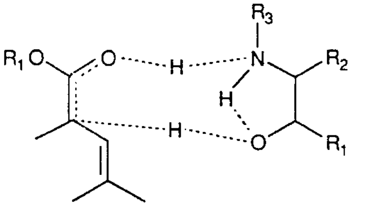
Scheme 9.5

Accordingly, apolar solvents, in particular *n*-hexane and dichloromethane, were found to be convenient for these enantioselective photodeconjugation reactions.

A variety of chiral *β*-amino alcohols bearing, e.g., secondary or tertiary amine groups, have been tested as organocatalysts [16, 17]. In particular, *β*-amino alcohols derived from (+)-camphor, e.g. **21**, were found to be very useful (Scheme 9.5) [17]. The size of the *N*-alkyl group of the organocatalyst is also very critical. The best results were obtained with (+)-camphor-derived catalysts, e.g. **21**, bearing a benzyl group or *iso*-propyl on the nitrogen atom, whereas larger or smaller *N*-substituents led to lower enantioselectivity [17].

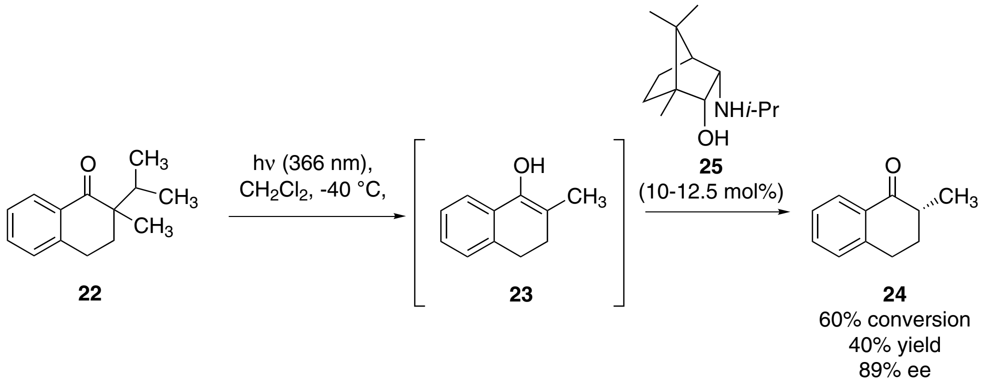
The transition state shown in Scheme 9.6 was also postulated by the Pete group [16]. Both functional groups of the *β*-amino alcohol catalyst play an important role in proton transfer by coordinating to the dienol. The resulting cyclic transition state is shown in Scheme 9.6. It is postulated that in this transition state abstraction of the hydroxyl proton from the dienol occurs in concert with protonation of the carbon in *α*-position by the hydroxyl group of the *β*-amino alcohol.

Enantioselective protonation reactions are not limited to dienols, however, but also function well with simple enols, e.g. the aryl enol **23**. The aryl enol **23** was



Scheme 9.6 (from Ref. [16] with permission of the ACS)

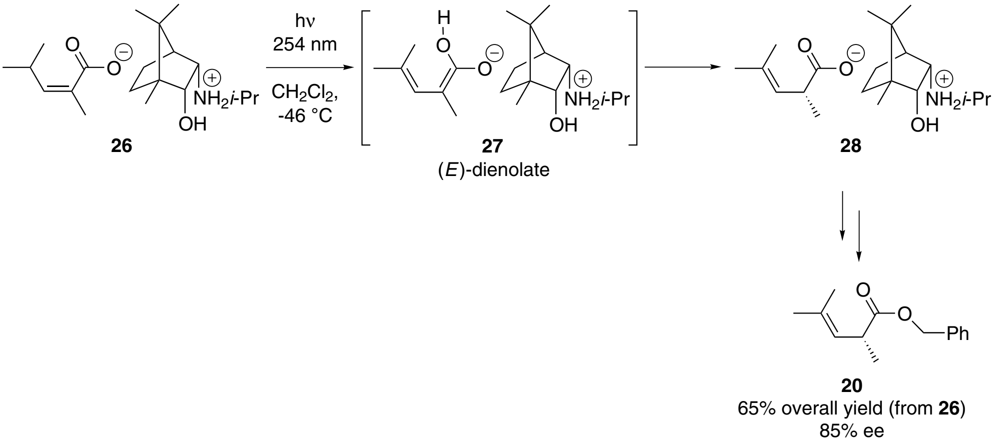
prepared *in situ* starting from **22** by means of a photoelimination reaction [19, 20]. Tautomerization was performed in the presence of a catalytic amount (10–12.5 mol%) of a chiral *β*-amino alcohol. This leads to optically active products of, e.g., type **24**, with enantioselectivity of 26–89% ee [20]. The highest enantioselectivity was obtained when the camphor-derived *β*-amino alcohol **25** was used as catalyst at −40 °C; the product **24** was obtained in 40% yield and with 89% ee (Scheme 9.7).



Scheme 9.7

9.3 Enantioselective Protonation of Enolates Generated *in situ* from Conjugated Unsaturated Carboxylates

The Muzart group reported an organocatalytic protonation reaction based on an *in situ*-formation of the required enolate by photochemical tautomerization of the chiral ammonium enolate **26** as an initial step [21]. The ammonium ion in **26** functions as the chiral proton source. Subsequent esterification affords the desired carboxylate **20** in up to 65% yield and enantioselectivity in the range 40–85% ee. An example is shown in Scheme 9.8. The best results were obtained by use of the secondary, *N*-isopropyl-substituted aminobornanol for formation of the chiral ammo-



Scheme 9.8

nium salt **26**. The preferred reaction temperature is −46 °C; at lower temperatures precipitation of the salt occurs.

Conclusion

In addition to asymmetric catalytic protonation using metal enolates, which has been found to be an efficient, widely applicable and highly enantioselective method for production of carboxylates bearing a stereogenic carbon center in the α-position, analogous organocatalytic reactions using enols or enolates in the absence of a metal component have been developed. These methods are based on use of an enol or enolate prepared *in situ* from a suitable precursor. Optically active β-amino alcohols have been successfully used as organocatalysts for enantioselective proton transfer. Medium to high enantioselectivity with ee values of up to 91% ee have been reached.

References

1 C. Fehr, *Angew. Chem.* **1996**, *108*, 2726–2748; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2566–2587.
2 A. Yanagisawa, H. Yamamoto in: *Comprehensive Asymmetric Catalysis, Volume 3*, Eds.: E. Jacobsen, A. Pfaltz, H. Yamamoto, Springer, Heidelberg, **1999**, chapter 34.2, p. 1295–1306.
3 B. Schäfer, *Chemie in unserer Zeit* **2002**, *36*, 382–389.
4 J. Eames, N. Weerasooriya, *Tetrahedron: Asymmetry* **2001**, *21*, 1–24.
5 H. Pracejus, *Liebigs Ann. Chem.* **1960**, *634*, 9–22.
6 H. Pracejus, G. Kohl, *Liebigs Ann. Chem.* **1969**, *722*, 1–11.
7 A. Tille, H. Pracejus, *Chem. Ber.* **1967**, *100*, 196–210.
8 H. Pracejus, F.-W. Wilcke, K. Hanemann, *J. Prakt. Chem.* **1977**, *319*, 219–229.
9 A. Kumar, R. V. Salunkhe, R. A. Rane, S. Y. Dike, *J. Chem. Soc., Chem. Commun.* **1991**, 485–486.
10 R. Henze, J. Duchamel, M.-C. Lasne,

Tetrahedron: Asymmetry **1997**, *8*, 3363–3365.

11 R. Mortezaei, O. Piva, F. Henin, J. Muzart, J.-P. Pete, *Tetrahedron Lett.* **1986**, *27*, 2997–3000.

12 O. Piva, F. Henin, J. Muzart, J.-P. Pete, *Tetrahedron Lett.* **1986**, *27*, 3001–3004.

13 J.-P. Pete, R. Mortezaei, F. Henin, J. Muzart, O. Piva, *Pure Appl. Chem.* **1986**, *58*, 1257–1262.

14 O. Piva, F. Henin, J. Muzart, J.-P. Pete, *Tetrahedron Lett.* **1987**, *28*, 4825–4828.

15 F. Henin, R. Mortezaei, J. Muzart, J.-P. Pete, O. Piva, *Tetrahedron* **1989**, *45*, 6171–6196.

16 O. Piva, R. Mortezaei, F. Henin, J. Muzart, J.-P. Pete, *J. Am. Chem. Soc.* **1990**, *112*, 9263–9272.

17 O. Piva, J.-P. Pete, *Tetrahedron Lett.* **1990**, *31*, 5157–5160.

18 J. Muzart, F. Henin, J.-P. Pete, A. M'Boungou-M'Passi, *Tetrahedron: Asymmetry* **1993**, *4*, 2531–2534.

19 F. Henin, J. Muzart, J.-P. Pete, A. M'Boungou-M'Passi, H. Rau, *Angew. Chem.* **1991**, *103*, 460–462; *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 416–418.

20 F. Henin, A. M'Boungou-M'Passi, J. Muzart, J.-P. Pete, *Tetrahedron* **1994**, *50*, 2849–2864.

21 F. Henin, S. Letinois, J. Muzart, *Tetrahedron: Asymmetry* **2000**, *11*, 2037–2044.

10
Oxidation

10.1
Epoxidation of Olefins

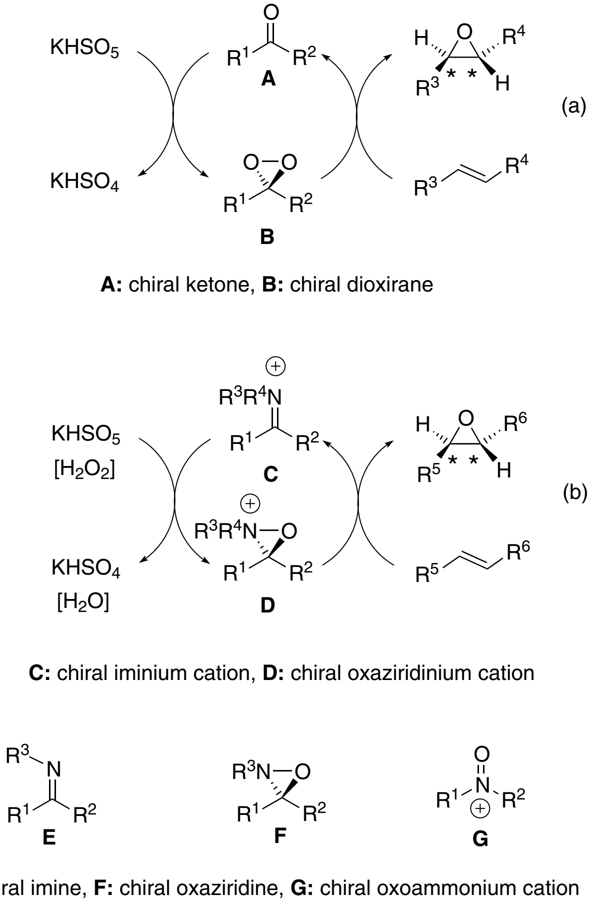
The asymmetric epoxidation of C=C double bonds provides access to enantiomerically enriched epoxides. The latter materials are of great practical value, in particular as intermediates in the production of enantiomerically pure pharmaceuticals. Recent years have seen the dramatic development of methods for this purpose. In the field of metal-catalyzed epoxidations, in particular, the titanium-catalyzed asymmetric epoxidation of allylic alcohols (Sharpless epoxidation) has found immense application in synthesis [1, 2]. Similarly, manganese–salen catalysts have proven their potential for asymmetric transformation of non-functionalized olefins (Jacobsen–Katsuki epoxidation) [3, 4]. For metal-free asymmetric epoxidation current methodology relies mainly on the development of chiral ketones **A** for catalytic generation of dioxiranes **B** as epoxidizing agents (Scheme 10.1, a). Potassium persulfate ($KHSO_5$) – in the form of its triple salt with K_2SO_4 and $KHSO_4$ ("Oxone", "Curox" etc.) – usually serves as the final oxidizing agent. Similarly, it has been reported that chiral iminium ions **C** enable generation of oxaziridinium cations **D** (Scheme 10.1, b). In these reactions either potassium persulfate or hydrogen peroxide served as the source of oxygen.

It should be noted that the related imine–oxaziridine couple **E**–**F** finds application in asymmetric sulfoxidation, which is discussed in Section 10.3. Similarly, chiral oxoammonium ions **G** enable catalytic stereoselective oxidation of alcohols and thus, e.g., kinetic resolution of racemates. Processes of this type are discussed in Section 10.4. Whereas perhydrates, e.g. of fluorinated ketones, have several applications in oxidation catalysis [5], e.g. for the preparation of epoxides from olefins, it seems that no application of chiral perhydrates in asymmetric synthesis has yet been found. Metal-free oxidation catalysis – achiral or chiral – has, nevertheless, become a very potent method in organic synthesis, and the field is developing rapidly [6].

10.1.1
Chiral Dioxiranes

The idea of using chiral ketones as catalysts for asymmetric epoxidation of olefins was first addressed by Curci et al. in the middle of the 1980s [7]. In this initial ex-

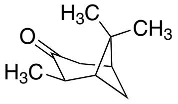
Asymmetric Organocatalysis. Albrecht Berkessel and Harald Gröger
Copyright © 2005 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim
ISBN: 3-527-30517-3

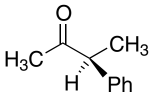


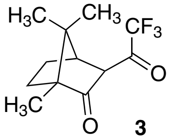
Scheme 10.1

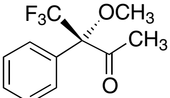
ample 20–300 mol% of ketones **1** and **2** were used and enantiomeric excesses of ca. 10% were reported for the epoxidation of *trans*-stilbene or *trans*-*β*-methylstyrene. In 1995 the same group reported ee up to 20% when the chiral ketones **3** and **4** were used in stoichiometric amounts [8]. Preparatively useful ee (e.g. 87% in the epoxidation of 4,4′-diphenyl-*trans*-stilbene) were achieved for the first time by Yang et al., who used equimolar amounts of the binaphthyl-derived ketone **5a** as the catalyst [9]. Subsequent studies enabled reduction of the catalyst loading to 10 mol% and revealed the importance of the "chiral selector" R in the ortho positions of the binaphthalene core structure [10, 11]. From these studies the bis-acetal **5c** emerged as a highly reactive and selective epoxidation catalyst (e.g. 93% yield and 84% ee in the epoxidation of *trans*-stilbene). The related C_2-symmetric ketones **6**–**8** were reported by Song et al. [12, 13] (ketone **7** also by Yang et al. [11]). The enantioselectivity of these materials was, however, lower than that of ketones **5a**–**c**,

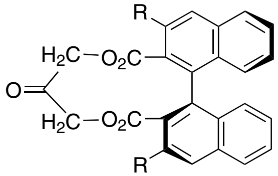
derived from 1,1′-binaphthyl-2,2′-dicarboxylic acids (best value 59% ee in the epoxidation of *trans*-stilbene by use of equimolar amounts of **8**).

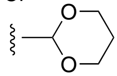

1

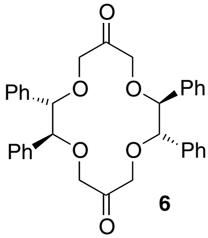

2

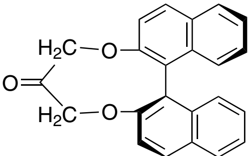

3

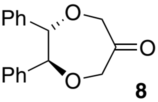

4



5a: R = H
5b: R = Cl
5c: R = 

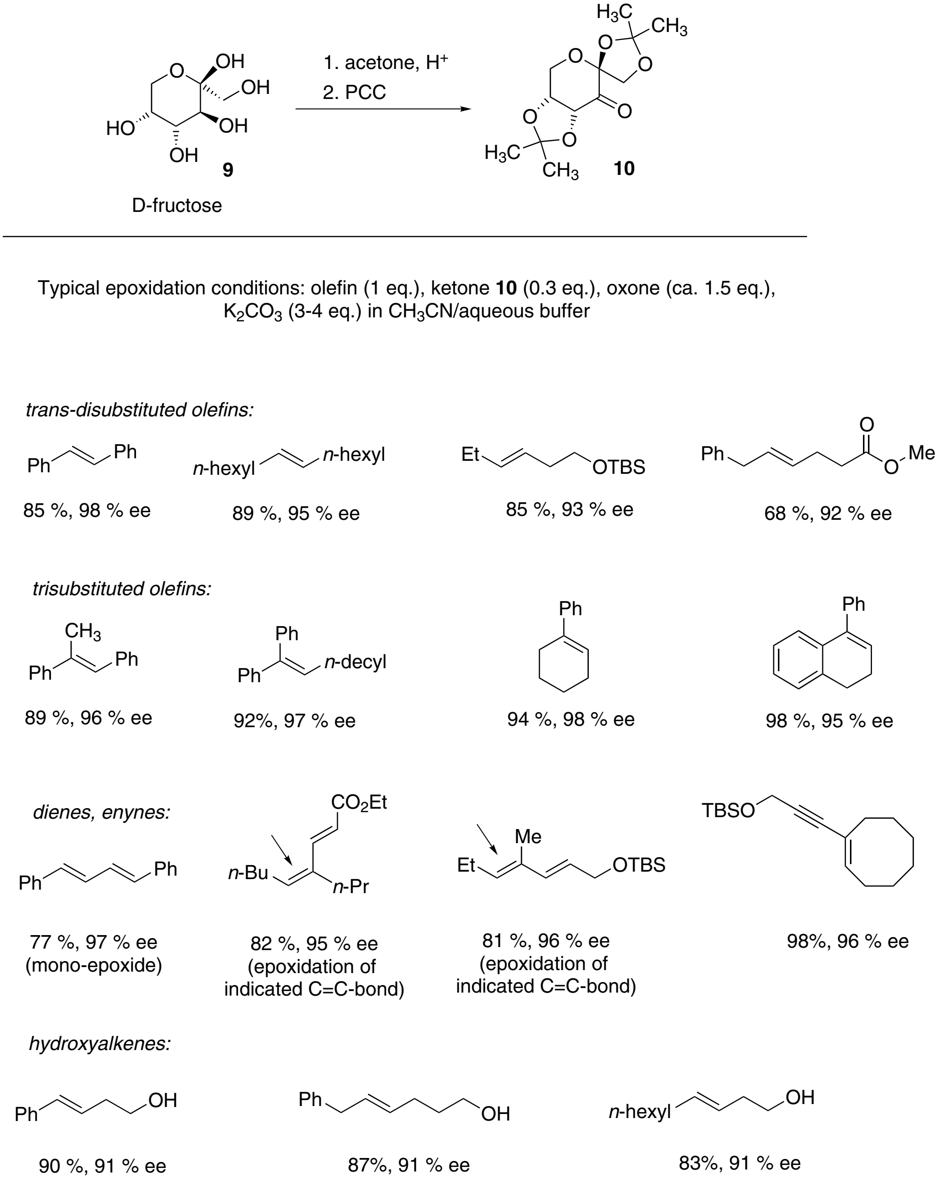

6


7


8

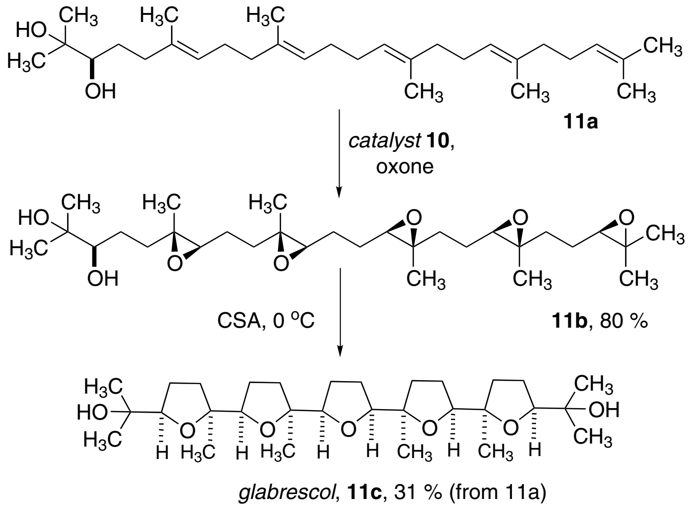
Ketones such as **5a–c** require rather expensive starting materials and several steps for their preparation. Consequently, the relatively high catalyst loadings (typically not less than 10 mol% relative to the substrate olefin) were disadvantageous for their broad application. This problem was solved by the introduction of the so-called Shi ketone **10** which can be prepared from inexpensive and readily available D-fructose **9** in two simple steps (Scheme 10.2) [14]. Ketone **10** is usually employed in buffered solutions at ca. 30 mol% loadings and mediates the asymmetric epoxidation of a variety of non-functionalized olefins with >90% ee [15, 16]. It should be noted that this catalyst – in the same way as the other chiral ketones already discussed – works particularly well on (*E*)-1,2-disubstituted and/or non-conjugated olefins which are less favorable substrates for the Jacobsen–Katsuki epoxidation [3, 4]. Trisubstituted olefins, dienes, enynes, and hydroxyalkenes can be epoxidized with >90% ee [17–19]. For the latter class of substrate it is worth noting that homoallylic or bis-homoallylic alcohols are not normally favorable substrates for the Sharpless epoxidation [1, 2]. One of the most impressive applications of the Shi catalyst **10** is the synthesis by Corey and Xiong of the pentacyclic oxasqualenoid glabrescol **11c** from dihydroxylated squalene **11a** in two steps only (Scheme 10.3) [20]. As a key step, the pentaene **11a** is converted enantioselectively to the pentaepoxide **11b**. On treatment with camphorsulfonic acid the latter is rearranged to the pentacyclic target molecule **11c**.

Oxidative degradation of the catalyst (e.g. lactone formation by Baeyer–Villiger oxidation) competes with oxygen transfer and is the reason a relatively high catalyst loading is required. In their search for more robust, yet (comparatively) readily available ketone catalysts, Shi et al. prepared the carbamates **12a–c** [20–22]. Use



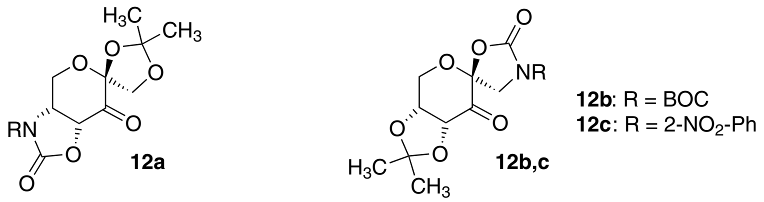
Scheme 10.2

of **12a** enables reduction of catalyst loading to 1–5% [20]. It was also found that ketones **12** (**12a**, R = BOC) afforded better ee in the epoxidation of *cis*-olefins and terminal olefins, classes of substrate less amenable to asymmetric epoxidation by the "classical" Shi-ketone **10** [22]. Some examples of olefins successfully epoxidized by the catalysts **12** are shown below. In addition, the glucose-derived carbamate ketones **12b,c** are also effective in the asymmetric epoxidation of *trans*-

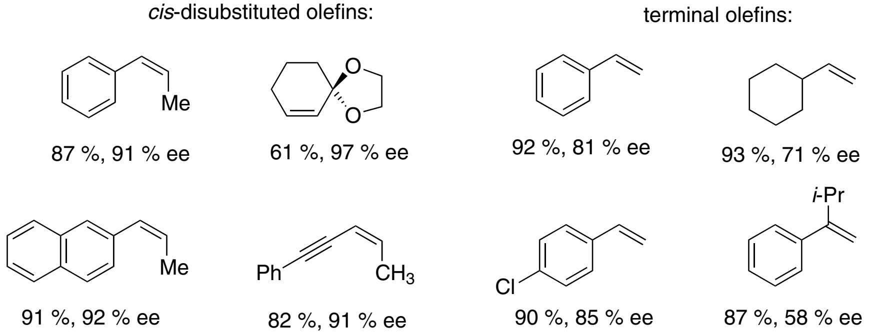


Scheme 10.3

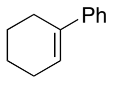
disubstituted or trisubstituted olefins. For example, *trans*-stilbene is transformed into its epoxide by catalyst **12b** in 65% yield and with 94% enantiomeric excess [21a].



Examples of epoxidations in the presence of 15-30 mol-% of the N-BOC carbamate catalyst **12b:**

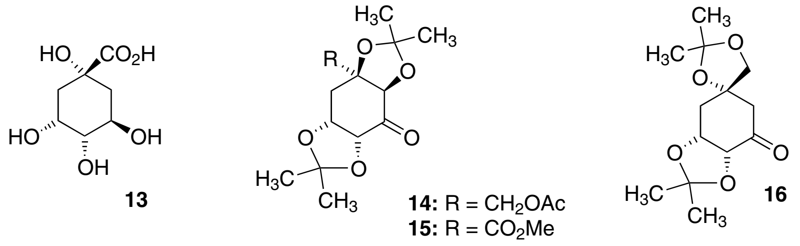


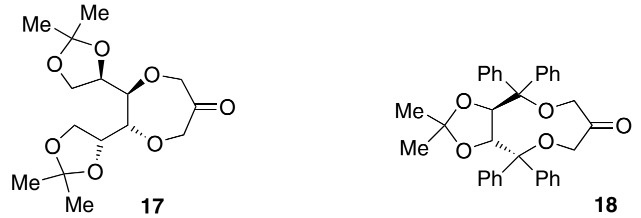
Comparison of the carbamate catalysts **12a** and **12b**:



12b: 68 %, 42 % ee
12c: 48 %, 59 % ee

Many other variations of the basic structure **10** have been explored, including anhydro sugars and carbocyclic analogs, the latter derived from quinic acid **13** [23–26]. In summary, the preparation of these materials (e.g. **14–16**) requires more synthetic effort than the fructose-derived ketone **10**. Occasionally, e.g. when using **14**, catalyst loadings can be reduced to 5% relative to the substrate olefin, and epoxide yields and selectivity remain comparable with those obtained by use of the fructose-derived ketone **10**. Alternative ex-chiral pool ketone catalysts were reported by Adam et al. The ketones **17** and **18** are derived from D-mannitol and tartaric acid, respectively [27]. Enantiomeric excesses up to 81% were achieved in the epoxidation of 1,2-(*E*)-disubstituted and trisubstituted olefins.

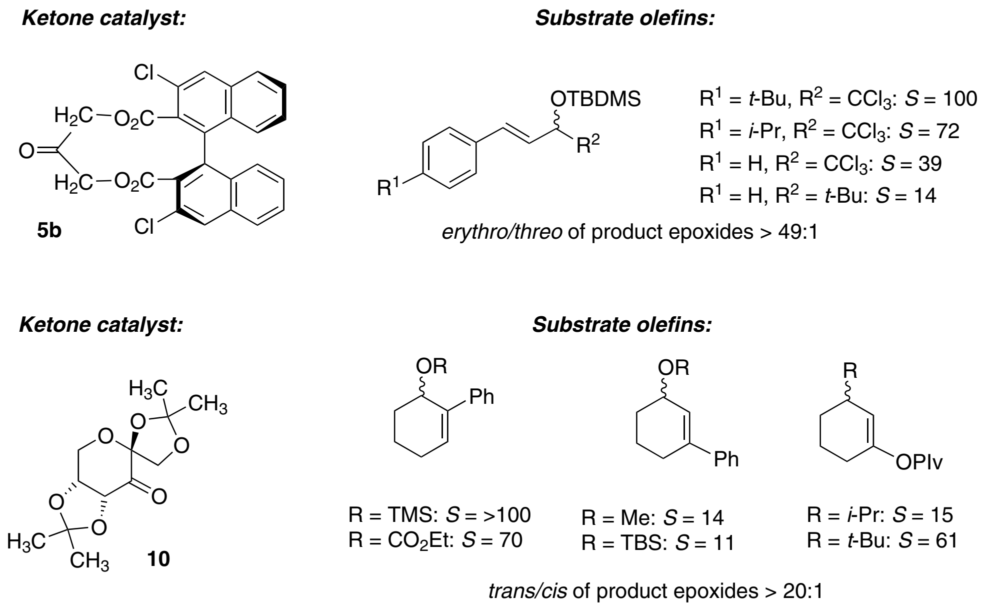




Chiral ketone catalysts of the Yang-type (**5a** and **5b**, see above) and of the Shi-type (**10**, Scheme 10.2) have been successfully used for kinetic resolution of several racemic olefins, in particular allylic ethers (Scheme 10.4) [28, 29]. Remarkable and synthetically quite useful *S* values of up to 100 (ketone **5b**) and above 100 (ketone **10**) were achieved. Epoxidation of the substrates shown in Scheme 10.4 proceeds with good diastereoselectivity. For the cyclic substrates investigated with ketone **10** the *trans*-epoxides are formed predominantly and *cis*/*trans*-ratios were usually better than 20:1 [29]. For the linear substrates shown in Scheme 10.4 epoxidation catalyzed by ketone **5b** resulted in the predominant formation of the *erythro*-epoxides (*erythro*/*threo*-ratio usually better than 49:1) [28].

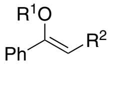
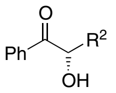
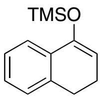
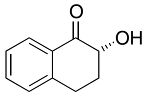
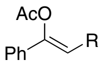
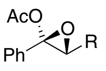
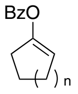
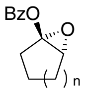
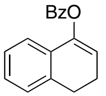
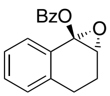
It should finally be pointed out that the mild reaction conditions typically employed in dioxirane-mediated oxidations enable the asymmetric epoxidation of enol ethers and enol esters. With the silyl ethers, work-up provides enantiomerically enriched α-hydroxy ketones. As summarized in Table 10.1, quite significant enantiomeric excesses were achieved by use of catalyst **10** at loadings ranging from 30 [30] to 300 mol% [31]. Enol esters afford the intact acyloxyepoxides; enantiomeric purities are, again, quite remarkable.

The fluorinated cyclohexanone derivatives **19a–d** were synthesized by Solladié-

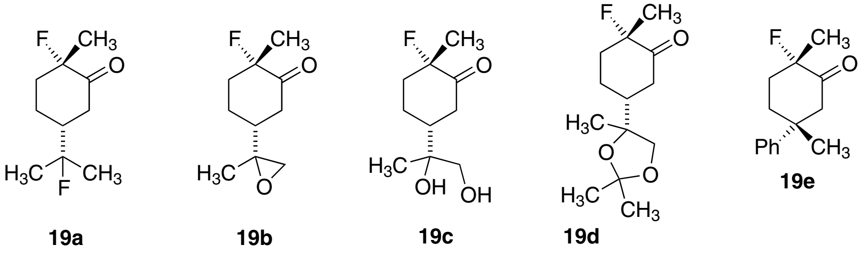


Scheme 10.4

Tab. 10.1

Substrate		*Product*	*Yield (%)*	*ee (%)*	*Ref.*
Enol ethers					
		R^1 = TBS, R^2 = CH_3	80	90	30
		R^1 = TBDMS, R^2 = CH_3	46	91	31
		R^1 = TMS, R^2 = CH_2CH_3	33	67	31
		R^1 = TMS, R^2 = Ph	36	61	31
			70	83	30
Enol esters					
		R = CH_3	66	91	30
		R = Ph	46	91	30
		n = 1	79	80	30
		n = 2	82	93	30
		n = 3	87	91	30
		n = 4	82	95	30
			92	88	30

Cavallo et al. from (+)-dihydrocarvone and evaluated in the asymmetric epoxidation of several silyl enol ethers [32]. Enantiomeric excess up to 74% was achieved in the epoxidation of the TBDMS *trans*-enol ether of desoxybenzoin with the fluoro ketone **19d** (30 mol% of the ketone catalysts). In earlier work Solladié-Cavallo et al. had shown that the fluoro ketones **19a** and **19e** can be used to epoxidize *trans*-stilbene with up to 90% ee (30 mol% ketone catalyst) [33]. Asymmetric epoxidation of *trans*-methyl 4-*para*-methoxycinnamate using ketone **19e** as catalyst is discussed in Section 10.2.

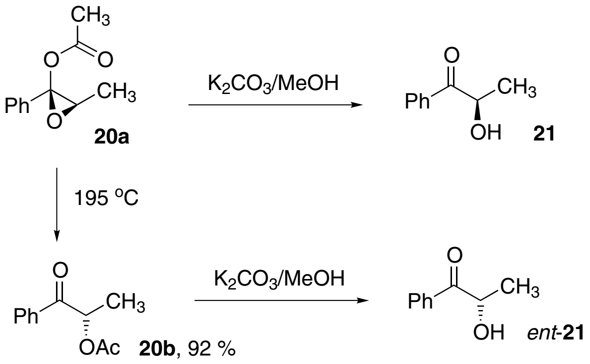


Epoxidations using oxone and 30 mol-% of the ketone catalysts **19**:

ketone **19d**, 90 %, 74 % ee

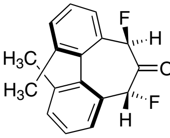
ketone **19a**, 90 %, 90 % ee
ketone **19e**, 95 %, 90 % ee

It is interesting to note that acyloxyepoxides can be converted to α-hydroxyketones with retention or inversion of configuration at C-α, depending on the reaction conditions chosen. As shown in Scheme 10.5, hydrolysis of epoxide **20a** leads



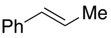
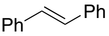
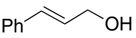
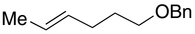
Scheme 10.5

Tab. 10.2



22

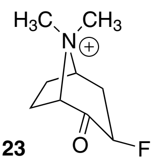
30 mol-% catalyst

Substrate	*Epoxide yield (ee)*
	80 (88)
	46 (94)
	93 (89)
	72 (68)

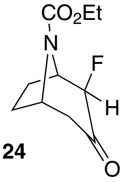
to the hydroxyketone **21** whereas heating of epoxide **20a** to 195 °C induces thermal rearrangement to the α-acetoxyketone **20b**. This process occurs with virtually no loss of enantiomeric purity. Hydrolysis of the acetoxyketone **20b** thus affords the α-hydroxyketone *ent*-**21** [30].

For ketones to effect oxygen transfer from caroate to organic substrates several delicate kinetic requirements must be fulfilled. First, addition of persulfate to the carbonyl carbon atom must occur. Second, subsequent decay of the Criegee intermediate must lead preferentially to the dioxirane and not to Baeyer–Villiger rearrangement of the ketone. Finally, the dioxirane must transfer an oxygen atom to the organic substrate, rather than unproductive caroate oxidation to molecular oxygen. Clearly, pH control is essential to prevent the latter side-reaction. For dioxirane formation to occur in preference to the competing Baeyer–Villiger oxidation the presence of electron withdrawing groups in the ketone's α-positions is essential. For example, for the Shi ketone **10** the acetal oxygen atoms provide this effect. As an alternative, fluorine substitution also has yielded quite effective enantioselective catalysts. For example, Denmark et al. have carefully studied the effects of fluorination on several cyclic ketones [34]. Their biphenyl-derived difluoro ketone **22** enables asymmetric epoxidation of several trans olefins (Table 10.2 [35]), including the non-conjugated benzyl (*E*)-4-hexenyl ether.

Fluoro ketones based on the tropinone skeleton and other bicyclo[3.2.1]octan-3-ones were studied by Denmark et al. (e.g. **23**) [34, 35] and Armstrong et al. (e.g. **24**) [36, 37]. Ketone **24** proved particularly efficient for asymmetric epoxidation of unfunctionalized olefins (Table 10.3).



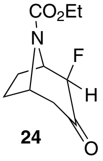
23



24

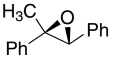
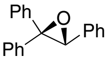
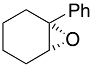
Catalyst **24** is, furthermore, readily accessible by means of a one-pot procedure consisting of asymmetric deprotonation of commercially available *N*-ethoxy-

Tab. 10.3



24

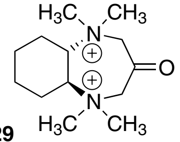
10 mol-% catalyst

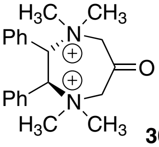
Product	Yield (%)	ee (%)
	88	76
	quant.	73
	quant.	83
	97	69

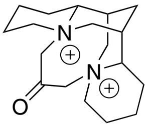
carbonyl-8-azabicyclo[3.2.1]-octane, trapping of the enolate anion with trimethylsilyl chloride, and subsequent α-fluorination by use of a SelectFluor reagent [38]. With ketone **23** 58% ee was achieved in the epoxidation of *trans*-stilbene [34b, 35].

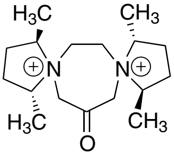
As summarized in Table 10.4, further studies by Armstrong et al. revealed that asymmetric epoxidation of *trans*-stilbene can also be effected by other bicyclic ketones (**25**–**28**) carrying electron withdrawing substituents in both the α-position and on the 1-bridge [35].

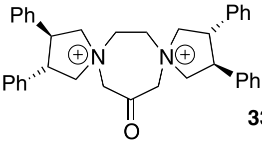
In the course of their exploration of structure–activity relationships for ketone catalysts, Denmark et al. noted that oxoammonium salts such as **29**–**33** are very efficient catalysts of the epoxidation of olefins [34a]. Unfortunately, enantiomeric excesses achieved with this class of ketone catalyst have not yet exceeded 40% (**30**, epoxidation of *trans*-β-methylstyrene). With the fluorinated oxoammonium catalyst **23** already mentioned, however, 58% ee was achieved in the asymmetric epoxidation of *trans*-stilbene [34b].

29 

 30

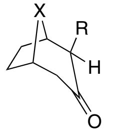
 31

32 

 33

Many attempts have been made to use hydrogen peroxide as the final oxidizing agent in ketone-catalyzed epoxidations. Because hydrogen peroxide itself does not convert ketones to dioxiranes, *in-situ* activation of the oxidant is necessary. Shi et al. have achieved this goal by using acetonitrile as a component of the solvent mixture

Tab. 10.4. Epoxidation of *trans*-stilbene catalyzed by α-substituted bicyclic ketones.



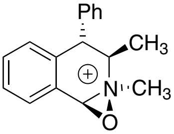
20-100 mol-% catalyst

Ketone	*Yield (%)*	*ee (%)*
24: R = F, X = N-CO_2Et	76	76
25: R = Cl, X = N-CO_2Et	41	54
26: R = OAc, X = N-CO_2Et	66	86
27: R = F, X = O	63	83
28: R = OAc, X = O	71	95

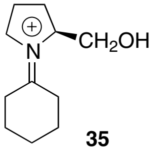
and simultaneously as activator, generating iminoperacetic acid *in situ* [39, 40]. In combination with the fructose-derived ketone **10** (see above), many prochiral olefins could be epoxidized with excellent enantioselectivity and considerable less production of salt by-products.

10.1.2
Chiral Iminium Ions

As shown in cycle (b) in Scheme 10.1, the iminium–oxaziridinium pair can also effect catalytic asymmetric epoxidation of alkenes. Early work in this field by Bohé et al. included investigation of the norephedrine-derived oxaziridinium salt **34** (33% ee in the catalytic epoxidation of *trans*-stilbene [41]; ee up to 61% was achieved when **34** was employed stoichiometrically [42]), or the L-proline-derived material **35** (39% ee in the epoxidation of *trans*-3-phenyl-2-propenol [43]). Rapid

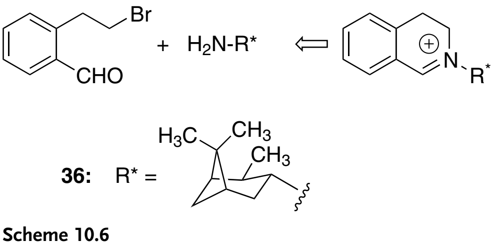


34



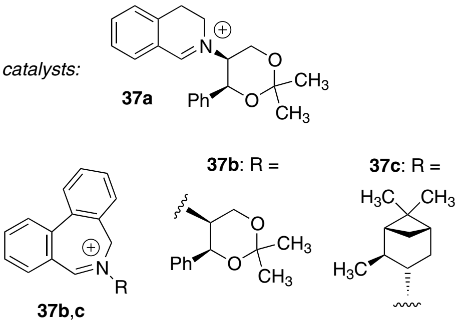
35

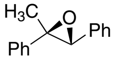
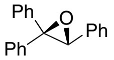
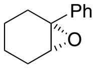
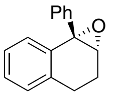
catalyst diversification was achieved by Page et al. by generating catalytically active iminium salts from a common, achiral bromoaldehyde precursor and readily available chiral primary amines (Scheme 10.6). The best enantioselectivity was achieved in the epoxidation of *trans*-stilbene (73% ee) by using the fenchylamine-derived catalyst **36** [44]. Further improvement was achieved with the iminium catalyst **37a** containing an acetal moiety (Table 10.5) [45]. Later, Page et al. described the dibenza-



Scheme 10.6

Tab. 10.5



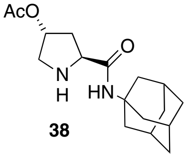
Product	*Catalyst (5 mol-%)*	*Yield (%)*	*ee (%)*
	37a	52	52
	37a 37b	54 90	59 59
	37a 37b	55 quant.	41 60
	37a 37b 37c	64 90 95	49 41 38

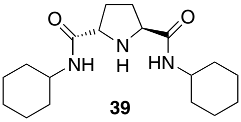
zepinium catalysts **37b** and **37c** [46]. As shown in Table 10.5, the performance of catalyst **37b** was best for both triphenylethene and 1-phenylcyclohexene as substrates. An attractive alternative to the *ex-situ* preparation of catalysts was found by Yang and Wong in the *in-situ* generation of iminium cations from aldehydes and secondary amines [47]. Clearly, this approach enables rapid screening of many aldehydes (for example **40**) and amines (for example **38** and **39**) to find the optimum combination for a given substrate. A summary of the two most efficient and selective aldehyde–amine combinations is given in Table 10.6.

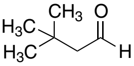
The binaphthyl-derived iminium-ion catalysts **41a** and **41b** were introduced by Aggarwal et al. [48a] and Page et al. [48b], respectively (Table 10.7). The highest enantioselectivities reported to date for an iminium-based olefin epoxidation – 95% ee using 1-phenyl-3,4-dihydronaphthalene as substrate – were achieved with the catalyst **41b** [48b].

The same group reported the striking observation that oxygen transfer from oxone to substrate olefins can also be catalyzed by *secondary amines alone* [49]. Pyrrolidines proved particularly efficient in this process, which was originally believed to involve the amine radical cation. Subsequent work [50, 51] identified the protonated amine as the active species and assigned a dual role to it. It is most probable that the ammonium cation acts both as a phase-transfer catalyst and forms a com-

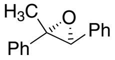
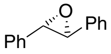
Tab. 10.6


38


39


40

50–100 mol-% of *in situ*-generated iminium catalyst

Amine	*Aldehyde*	*Product epoxide*	*Yield (%)*	*ee (%)*
38	40		99	59
39	40		93	65

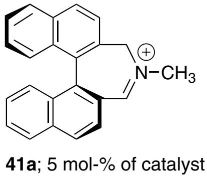
plex with the persulfate anion in which the latter is activated for oxygen transfer [51]. When the hydrochloride of the chiral pyrrolidine (*S*)-diphenylmethylpyrrolidine was used as catalyst (10 mol%, 2 equiv. oxone, −10 °C), 1-phenylcyclohexene was converted to its epoxide in high yield and with 52% ee. Up to 66% ee was achieved with the analogous bis-naphthylmethylpyrrolidine [51]. It is hoped that this remarkably simple process can be further improved and find wider application.

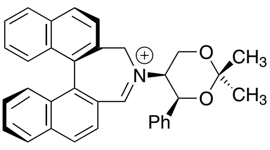
Conclusions

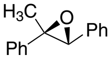
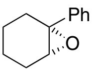
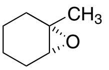
Both chiral ketones and chiral iminium salts have proven their potential as metal-free enantioselective catalysts of epoxidation. The enantiomeric excesses currently observed with chiral ketones are higher than those achieved with iminium salts. In terms of practicability, the Shi ketone **10**, an inexpensive and readily available

Tab. 10.7

catalysts:


41a; 5 mol-% of catalyst


41b; 0.1 - 5 mol-% of catalyst

Product[a]	*Catalyst*[a]	*Yield (%)*	*ee (%)*
	41a	60	45
	41b	58	49
	41a	80	71
	41b	69	91
	41a	80	39

a) Major enantiomer for catalyst **41a**; opposite major enantiomer for **41b**.

material, probably still has the most potential for broad application in organic synthesis.

10.2
Epoxidation of Enones and Enoates

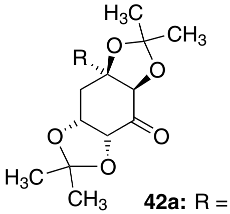
As discussed in Section 10.1, asymmetric epoxidation of C=C double bonds usually requires electrophilic oxygen donors such as dioxiranes or oxaziridinium ions. The oxidants typically used for enone epoxidation are, on the other hand, nucleophilic in nature. A prominent example is the well-known Weitz–Scheffer epoxidation using alkaline hydrogen peroxide or hydroperoxides in the presence of base. Asymmetric epoxidation of enones and enoates has been achieved both with metal-containing catalysts and with metal-free systems [52–55]. In the (metal-based) approaches of Enders [56, 57], Jackson [58, 59], and Shibasaki [60, 61] enantiomeric excesses > 90% have been achieved for a variety of substrate classes. In this field, however, the same is also true for metal-free catalysts. Chiral dioxiranes will be discussed in Section 10.2.1, peptide catalysts in Section 10.2.2, and phase-transfer catalysts in Section 10.2.3.

10.2.1
Chiral Dioxiranes

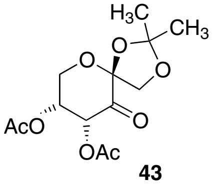
As shown in Scheme 10.7, the ketone catalysts **42a** and **42b** developed by Shi et al. enable asymmetric epoxidation of the enones **45a–c** in good yields and enantiomeric excesses up to 96% [62, 63]. Oxone is employed as the final oxidizing agent, and catalyst loadings are typically 10 mol% (relative to the substrate). In subsequent work, Shi et al. identified the carbohydrate ketone **43** as a highly effective catalyst for asymmetric epoxidation of enoates [63]. As shown in Scheme 10.7, many di- and trisubstituted enoates **46a–f** could be epoxidized with enantiomeric excesses > 90% [63]. Asymmetric epoxidation of the cinnamate **46a** was also achieved by use of the tropinone derivative **44**, introduced by Armstrong and Hayter (64% ee for the methyl ester, Scheme 10.7) [64]. Solladié-Cavallo and Bouérat reported the asymmetric epoxidation of methyl *para*-methoxycinnamate (ee up to 66%) with a chiral fluorocyclohexanone as catalyst [65a,b]. (The structure of the fluoroketone **19e** used in this study is given in Section 10.1.1.) See ref. 65c for a recent report by Seki and Imashiro on the use of ketone **5a** for the same transformation (80% ee).

10.2.2
Peptide Catalysts

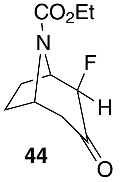
In the early 1980s, Juliá and Colonna reported that the Weitz–Scheffer epoxidation of chalcone (**45a**) can be catalyzed by poly-amino acids such as poly-L-alanine, and that the resulting epoxide is formed with enantiomeric excesses > 90% (Scheme 10.8) [66]. In the original three-phase procedure the enone is dissolved in an



42a: R = CH_2OAc
42b: R = $C(CH_3)_2OH$



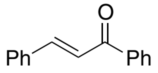
43



44

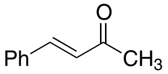
Typical epoxidation conditions: olefin (1 eq.), ketone (10-30 mol-%), oxone (ca. 2-5 eq.), K_2CO_3 (5-6 eq.) or $NaHCO_3$ (up to 15.5 eq.) in CH_3CN/aqueous buffer

enones:



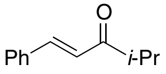
45a

ketone **42a:** 80 %, 94 % ee
ketone **42b:** 85 %, 96 % ee



45b

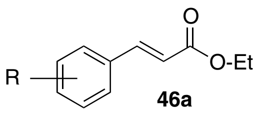
75 %, 82 % ee (ketone **42b**)



45c

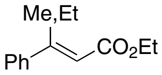
70 %, 89 % ee (ketone **42b**)

enoates:

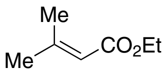


46a

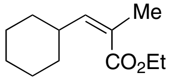
catalyst **42a**: 34 %, 86 % ee (R = H)
catalyst **42b**: 35 %, 89 % ee (R = H)
catalyst **43** : R = H, *o,p*-Me, *p*-Cl, *p*-MeO *o,m,p*-F, *p*-Cl: 40-91 %, 93-97 % ee
catalyst **44** : R = H (methyl ester): 33 %, 64 % ee



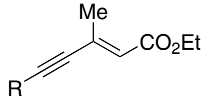
46b, catalyst **43**: 91-93 %, 93-96 % ee



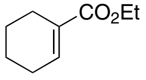
46c, catalyst **43**: 64 %, 82 % ee



46d, catalyst **43**: 77%, 89 % ee

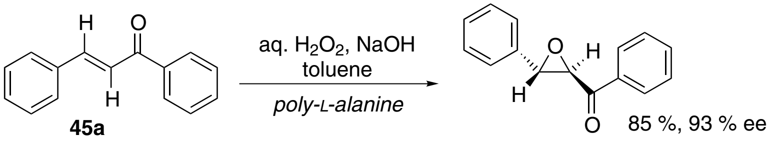


46e, catalyst **43**: R = Ph, TMS, *n*-Bu: 74-96 %, 94-98 % ee



46f, catalyst **43**: 77%, 93 % ee

Scheme 10.7



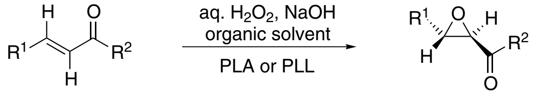
Scheme 10.8

organic solvent such as toluene or dichloromethane, and alkaline aqueous hydrogen peroxide (30%) serves as the oxygen donor. The insoluble poly-amino acid forms a third phase. The reaction is performed at room temperature, no inert atmosphere is needed, and both reagents and catalyst are inexpensive and readily available.

Because the catalyst is usually prepared by the polymerization of amino acid *N*-carboxy anhydrides, induced by water or amines [66, 67], the Juliá–Colonna epoxidation was soon recognized as a reaction of great practical value. In the course of exploration of the scope of the Juliá–Colonna procedure many enone substrates were successfully epoxidized by use of the original three-phase conditions (Table 10.8).

Clearly, using a poly-D-amino acid instead of the corresponding poly-L-amino

Tab. 10.8

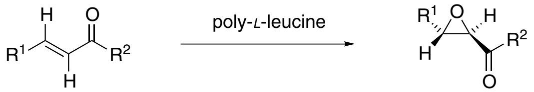


PLA: poly-L-alanine; PLL: poly-L-leucine

R¹	*R²*	*Catalyst*	*Yield (%)*	*ee (%)*	*Ref.*
Ph	Ph	PLA	85	93	67
Ph	*o*-MeOC_6H_4	PLA	54	50	66
Ph	2-naphthyl	PLL	90	93	68
Ph	2-furyl	PLL	85	87	68
Ph	2-thienyl	PLA	96	80	66
Ph	2-pyridyl	PLL	74	79	68
Ph	*t*-butyl	PLL	92	>98	68
Ph	cyclopropyl	PLL	85	77	69
o-[Ph$(CH_2)_8$]C_6H_4	2-naphthyl	PLL	82	95	70
p-MeSC_6H_4	2-naphthyl	PLL	65	96	71
2-furyl	2-naphthyl	PLL	75	>96	68
4-pyridyl	2-naphthyl	PLL	67	>96	68
2-pyridyl	Ph	PLL	84	72	68
t-butyl	Ph	PLL	85	90	68
PhCO	Ph	PLL	76	76	69
t-BuO_2C	Ph	PLL	66	>95	69
t-BuCO	*t*-butyl	PLL	>95	>95	69
n-Bu_3Sn	Ph	PLL	90	>99	72
β-styryl	2-naphthyl	PLL	78	>96	68
β-styryl	*t*-butyl	PLL	90	>97	68

acids affords the product epoxide of opposite absolute configuration [71]. It should be noted that the substrates listed in Table 10.8 not only encompass chalcone derivatives, but also dienones, enediones, unsaturated ketoesters, and β-stannylenones. Nevertheless, it became evident soon after its discovery that the Juliá–Colonna epoxidation in its original form suffers from three drawbacks: (i) its substrate spectrum is rather narrow, i.e. limited to (E)-enones, and no asymmetric epoxidation of, e.g., cycloalkenones is feasible; (ii) reaction times were long, usually in the range of 1 to 3 days; and (iii) the poly-amino acid turns into a gel during the reaction which makes catalyst separation and repeated use difficult. Whereas the problem of limited substrate spectrum still needs improvement, significant advances have been made with regard to reaction times and catalyst activity, and separation of the reaction mixture from the poly-amino acid catalyst. Reaction times were reduced from days to less than an hour by development of so-called two-phase reaction conditions. In this procedure the epoxidation is performed under anhydrous conditions in THF as solvent, the urea–hydrogen peroxide (UHP) clathrate is the source of oxygen, and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) serves as a strong homogeneously soluble base [73, 74]. As summarized in Table 10.9, enolizable ketones (R^2 = methyl, ethyl, n-propyl, i-propyl, i-butyl) can also be epoxidized under these conditions, which is not true for the original three-phase procedure.

Tab. 10.9



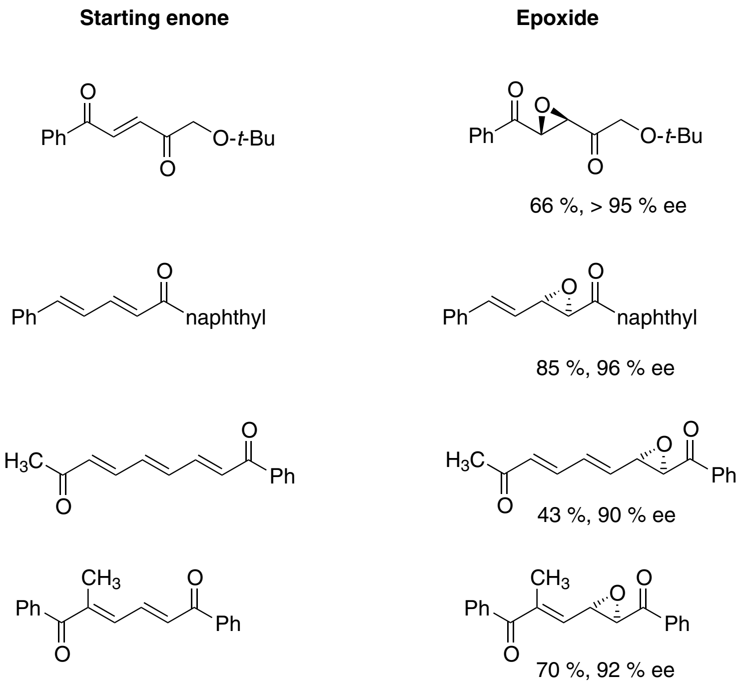
Methods: **A:** poly-L-leucine, urea-H_2O_2, DBU, THF
B: poly-L-leucine, sodium percarbonate, DME, water
C: poly-L-leucine on SiO_2, urea-H_2O_2, DBU, THF

R^1	R^2	*Method*	*Yield (%)*	*ee (%)*	*Ref.*
Ph	Ph	A	85	>95	73
		B	87	94	75
		C	quant.	>93	79
Ph	o-$O_2NC_6H_4$	A	91	91	81
Ph	o-$H_2NC_6H_4$	A	81	>98	81
		C	85	93	79
Ph	2-naphthyl	A	91	91	76
Ph	ethyl	A	80	82	76
Ph	methyl	A	70	80	73
Ph	*n*-propyl	A	85	94	76
Ph	*i*-propyl	A	56	89	79
		C	78	93	79
Ph	*i*-butyl	A	87	96	76
Ph	*t*-butyl	A	76	94	73
		B	94	94	75
cyclo-hexyl	Ph	A	91	89	73
β-styryl	2-naphthyl	A	85	96	82

Disadvantages are that the UHP/DBU/THF system is substantially more expensive than the original three-phase system and the over-stoichiometric use of DBU as base might be problematic for large-scale applications. As a third possibility the use of sodium percarbonate – as both base and oxidant – in DME–water mixtures was investigated and optimized [75]. Whichever of these systems is used, activation is necessary to achieve optimum performance of the poly-amino acid catalyst; this entails stirring with aqueous sodium hydroxide and toluene at room temperature for several days [75, 76]. Poly-L-leucine is usually employed as catalyst, but higher rates and enantioselectivity have sometimes been reported for poly-L-neopentylglycine [77].

Further improvement both of the activity of the catalyst and of its ease of handling and recycling was achieved by immobilization on polystyrene supports [78] and, in particular, on silica gel [79, 80]. The latter procedure affords "poly-amino acids on silica catalysts", the so-called "PaaSiCats". The silica-supported peptide catalysts are sufficiently active to enable use of catalyst loadings as low as 2.5 mol% (one equivalent corresponds to one poly-amino acid chain).

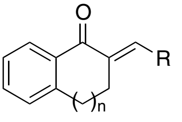
It has been mentioned already that "simple" acylic enones are not the only class of substrate amenable to poly-amino acid catalyzed epoxidation. More complex structures and their epoxidation products are shown in Scheme 10.9 [71, 82, 83].



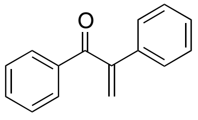
Reagents: poly-*L*-leucine, urea-hydrogen peroxide, DBU, THF

Scheme 10.9

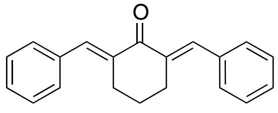
There are also a few examples of poly-amino acid catalyzed epoxidation of non-linear enones. These include tetralone derivatives **47**, which can be epoxidized with good yields and enantiomeric excesses; the best results were achieved for R = *p*-O_2N-C_6H_4 and $n = 1$ (85%; 96% ee) [84]. Other examples are the epoxidation of "iso-chalcone" **48** (78%; 59% ee) [69] or of bis-benzylidene cyclohexanone **49**, which affords the corresponding bis-epoxide "of good optical purity" [69].



47

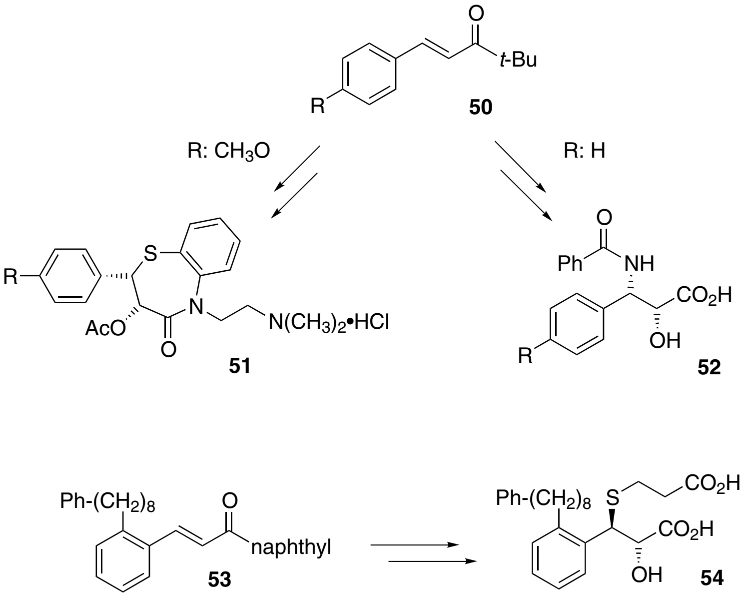


48

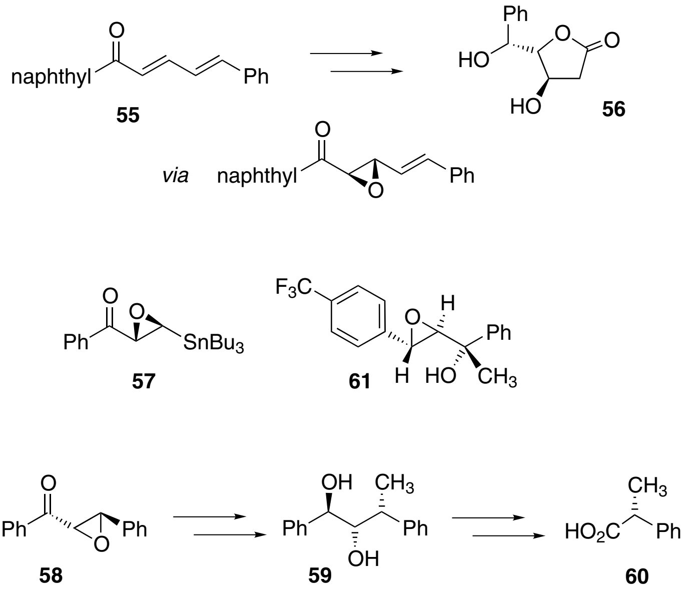


49

The enantiomerically pure epoxyketones resulting from poly-amino acid-catalyzed epoxidation are versatile intermediates for synthesis of more complex target molecules. For example, the enones **50** have served as starting materials for enantioselective synthesis of diltiazem **51** and the Taxol side-chain **52** (Scheme 10.10) [73]. Similarly, the leukotriene antagonist **54** (SK&F 104353) was prepared from the chalcone derivative **53** [70]. After asymmetric epoxidation, the subsequent steps in the syntheses of **51**, **52**, and **54** are nucleophilic opening of the epoxide ring and Baeyer–Villiger oxidation of the ketones to the corresponding esters [85]. The latter step is necessary because the poly-amino acid catalyzed epoxidation of electron-poor olefins works at best poorly on cinnamates, compared with the excel-



Scheme 10.10



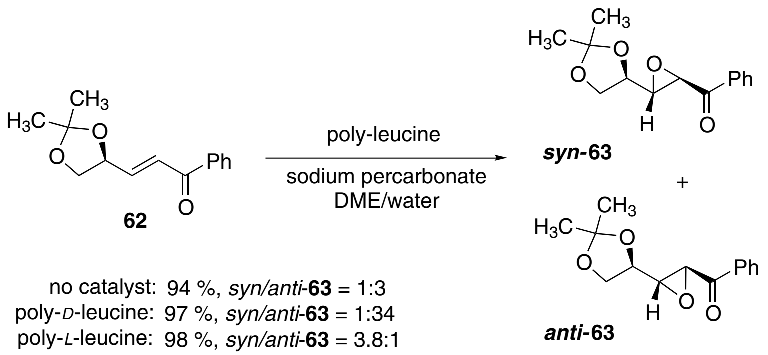
Scheme 10.11

lent results obtained with enones. Similarly, intramolecular epoxide opening provides access to, e.g., enantiomerically pure flavonoids [86, 87].

When dienones such as **55** are subjected to the epoxidation conditions the electron-poorer C=C double bond is selectively epoxidized. The other C=C bond can be functionalized further, for example, it can be dihydroxylated, as shown in the synthesis of the lactone **56** (Scheme 10.11) [82]. Stannyl epoxides such as **57** (Scheme 10.11, see also Table 10.8, $R^1 = n\text{-}Bu_3Sn$) can be coupled with several electrophiles [72], reduction of chalcone epoxide **58** and ring opening with alkyl aluminum compounds provides access to, e.g., the diol **59** and to phenylpropionic acids (for example **60**). Tertiary epoxy alcohols such as **61** can be obtained with excellent diastereoselectivity by addition of Grignard reagents to epoxy ketones [88, 89].

Finally, it should be mentioned that poly-amino acid catalysts have been used either to enhance or override substrate-induced diastereoselectivity in the Weitz–Scheffer epoxidation of chiral enones (Scheme 10.12) [90].

All peptide-catalyzed enone epoxidations described so far were performed using insoluble, statistically polymerized materials (neat or on solid supports). One can, on the other hand, envisage: (i) generation of solubilized poly-amino acids by attachment to polyethylene glycols (PEG); and (ii) selective construction of amino acid oligomers by standard peptide synthesis–linked to a solid support, to a soluble PEG, or neat as a well-defined oligopeptide. Both approaches have been used. The former affords synthetically useful and soluble catalysts with the interesting feature that the materials can be kept in membrane reactors for continuously oper-



Scheme 10.12

ated epoxidation reactions [91, 92]. It is interesting to note that the average number of amino acid residues necessary for satisfactory enantioselection is lower when the peptides are bound to PEG (8–10) compared with free oligo amino acids (ca. 20) [91, 92].

Well-defined peptides of known sequence have been used to shed light on the mechanism of catalysis in the epoxidation of enones with hydrogen peroxide [91, 93–95]. The peptide sequences of the catalysts have been systematically varied and correlated with catalytic activity and selectivity. From the many variations investigated it was concluded: (i) that the *N*-terminal region of the peptides harbors the catalytically active site, and that (ii) a helical conformation is required for the peptide catalysts to be active. The latter conclusion is supported both by the dependence of catalytic activity on chain-length and by IR investigations [91, 94]. NMR data that might aid further elucidation of catalyst structure, interaction with the substrate enones, etc., are, unfortunately, not yet available.

Berkessel et al. recently presented a mechanistic model for the asymmetric epoxidation of chalcone catalyzed by solid-phase-bound leucine oligomers [95]. They synthesized the whole series of L-leucine 1–20-mers bound to TentaGel S NH_2, plus inverse L-leucine oligomers (i.e. bound to the solid support via the *N*-terminus) and a series of solid-phase-bound *β*-peptides Subsequent assessment of the catalytic activity revealed that for the L-leucine oligomers, no more than 4 or 5 amino acid residues are necessary for full enantioselection (96–98% ee) and that catalyst activity increases with increasing chain length. From all the experiments is was concluded that the three non-intra-helical N–H bonds present at the *N*-terminus play a crucial role in the catalytic mechanism. On the basis of results from molecular modeling studies Berkessel et al. suggest that the carbonyl oxygen atom of the enone substrate is hydrogen-bonded to the NH of the amino acids at the *N*-terminus and at position $n-2$, and that the hydroperoxide nucleophile is delivered by the NH group of amino acid $n-1$. Consequently, the sense of helicity of the peptide catalyst determines the sense of induction in the epoxidation reaction. Figure 10.1 illustrates the binding of chalcone to the *N*-terminus of the pep-

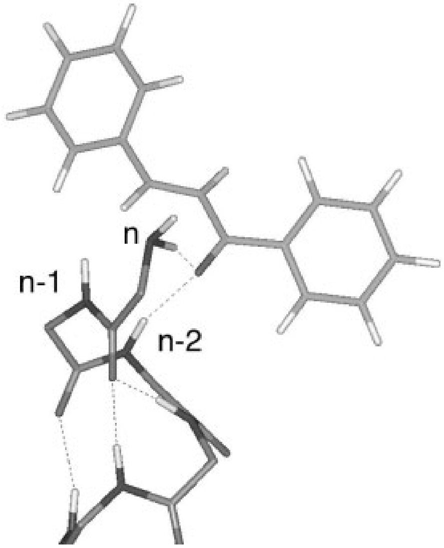


Fig. 10.1

tide and Figure 10.2 shows how a hydroperoxide anion, bound to the NH of amino acid $n-1$ is delivered face-selectively to the β-carbon atom of the bound substrate (chalcone). According to this model the action of the peptide catalysts used in the Juliá–Colonna epoxidation bears much similarity to that of enzymes, in particular the binding/activation and proper orientation of the substrates which ultimately effects the excellent enantioselectivity of the overall process.

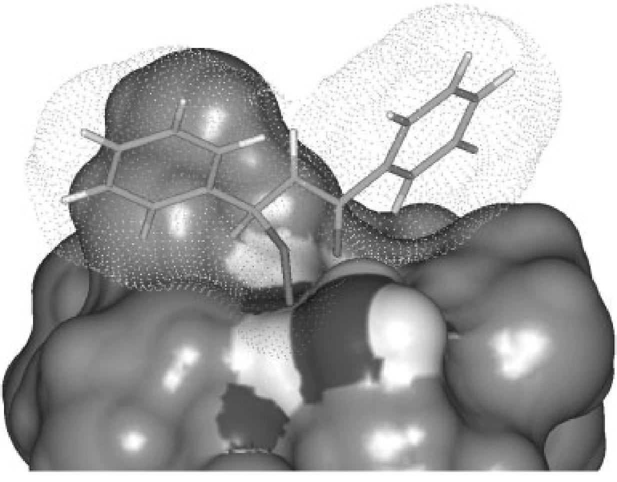
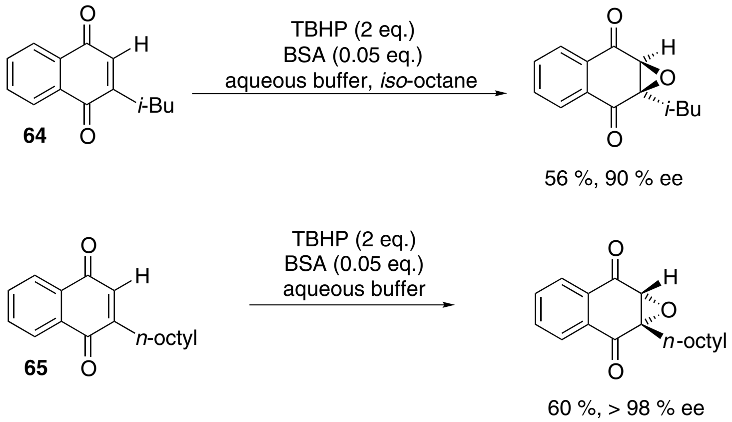


Fig. 10.2



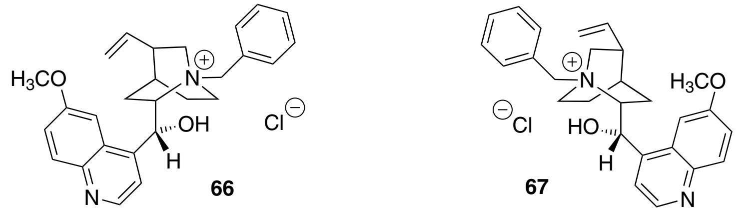
Scheme 10.13

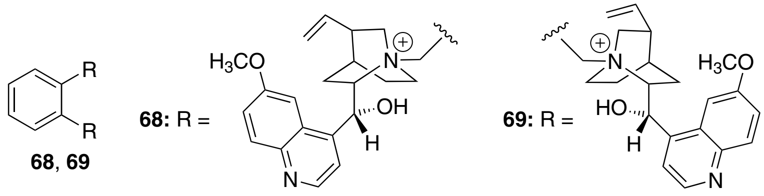
In an approach to using naturally occurring and readily available larger peptides as catalysts, Colonna et al. investigated the effect of bovine serum albumin on the Weitz–Scheffer epoxidation of naphthoquinones [96–99]. They found that 2-isobutylnaphthoquinone (**64**) and 2-*n*-octylnaphthoquinone (**65**) could be epoxidized with *tert*-butylhydroperoxide (TBHP) as oxidant in good yields and high enantioselectivity (Scheme 10.13). Unfortunately, as one might expect, minor changes to the structure of the substrate strongly affect both the activity and the selectivity with which the albumin catalyst effects the epoxidation.

10.2.3
Phase-transfer Catalysis

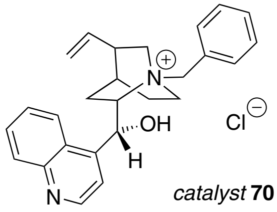
Phase-transfer catalysis has been widely been used for asymmetric epoxidation of enones [100]. This catalytic reaction was pioneered by Wynberg et al., who used mainly the chiral and "pseudo-enantiomeric" quaternary ammonium salts **66** and **67**, derived from the cinchona alkaloids quinine and quinidine, respectively [101–105].

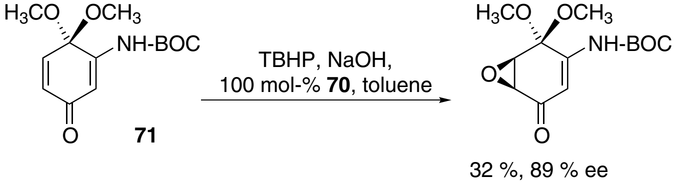
Phase-transfer catalysts of this type enabled the epoxidation of enones using hydrogen peroxide, TBHP, or sodium hypochlorite as the sources of oxygen. Although in this work enantiomeric excesses did not exceed 54%, Onda et al. later reported that catalyst **66** afforded 78% ee in the epoxidation of 2-(2-carbomethoxyphenyl)naphthoquinone [106]. It is worthy of note that the phase-transfer procedure enables asymmetric epoxidation of cyclohexenone and derivatives, which is not possible with the peptide catalysts discussed in Section 10.2.2. Kawaguchi, Oda, Baba et al. reported the synthesis of the "dimeric" phase-transfer catalysts **68** and **69** and of a monomeric quinine derivative with a fluorenyl group on the quaternary nitrogen atom. Up to 63% enantiomeric excess was in the epoxidation of cyclohexenone [107–109]. More recent work by Taylor et al. involved the cinchonidi-





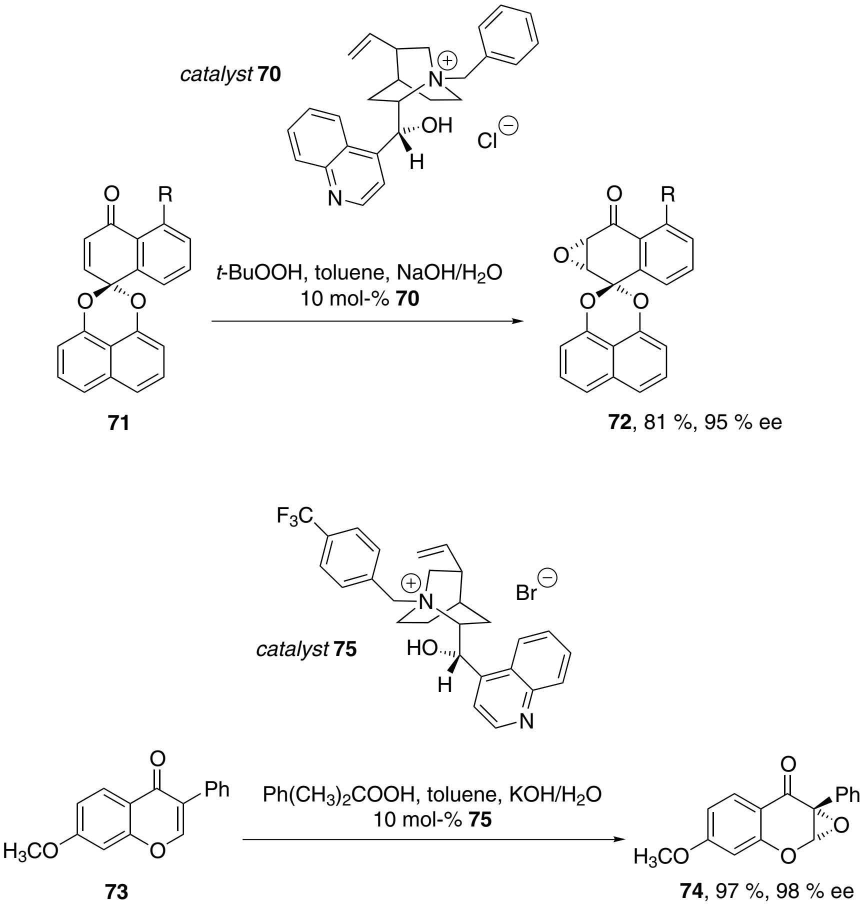
nium cation **70** [110, 111]. In the asymmetric epoxidation of the quinone acetal **71**, 89% ee could be achieved, albeit at a catalyst loading of ca. 100 mol% (Scheme 10.14).





Scheme 10.14

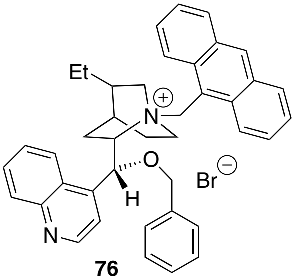
The *N*-benzylcinchonidinium catalyst **70** was successfully employed by Barrett et al. in the synthesis of (−)-preussomerin G [112]. As a key step the epoxide **72** was obtained from the quinone acetal **71** in 81% yield and with 95% ee in the presence of 10 mol% of the ammonium salt **70** (Scheme 10.15). Adam et al. recently reported the highly enantioselective epoxidation of isoflavones [113]. The best results, i.e. ee up to 98% with essentially quantitative yields, were achieved when



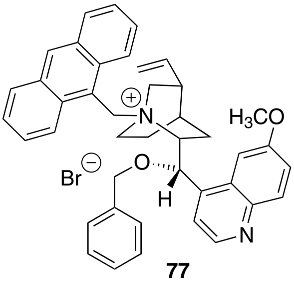
Scheme 10.15

the substrate **73** was transformed into the epoxide **74** in the presence of the trifluoromethylated catalyst **75** (Scheme 10.15) [113, 114].

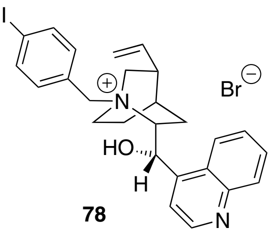
A further significant improvement of alkaloid-derived phase-transfer catalysts was reported by Lygo et al. [115–117]. In their approach, the cationic nitrogen atom carries a (9-anthracenyl)methyl substituent and the secondary hydroxyl group of the alkaloid nucleus is benzylated (**76**, **77**). Results obtained with the catalysts **76** and **77** are summarized in Table 10.10. It should be noted that the ammonium salt was also employed by Corey at al., in conjunction with lower reaction temperatures and potassium hypochlorite as the final oxidizing agent [118]. Arai et al. have also investigated the alkylation of cinchonine with a number of substituted benzyl halides [119, 120a,b]. In the epoxidation of chalcone, the para-iodobenzylated catalyst **78** proved best (Table 10.10). For the highly enantioselective epoxidation of enones using the binaphthyl-based Marvoka-catalysts (up to 99% ee), see ref. 120c.



76



77



78

Tab. 10.10

Methods: **A**: 10 mol-% catalyst 76, NaOCl, 25 °C (Refs. 115–117)
B: 10 mol-% catalyst **77**, KOCl, −40 °C (Ref. 118)
C: 5 mol-% catalyst 78, H_2O_2, LiOH, 4 °C (Refs. 119, 120)

R¹	*R²*	*Method*	*Yield (%)*	*ee (%)*
Ph	Ph	A	90	86
		B	96	93
		C	97	84
Ph	*p*-BrC_6H_4	A	99	88
		B	92	93
p-$H_3COC_6H_4$	Ph	A	87	82
		B	70	95
m-$H_3CC_6H_4$	Ph	C	quant.	82
n-C_6H_{13}	*p*-BrC_6H_4	A	89	84
n-C_5H_{11}	*p*-FC_6H_4	B	90	91
c-C_6H_{11}	Ph	B	85	94

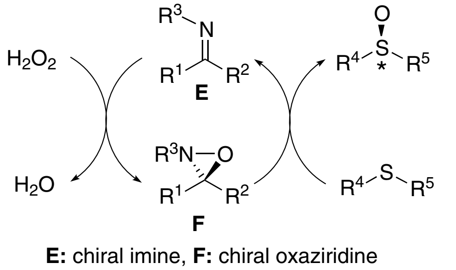
Conclusions

In the metal-free epoxidation of enones and enoates, practically useful yields and enantioselectivity have been achieved by using catalysts based on chiral electrophilic ketones, peptides, and chiral phase-transfer agents. (*E*)-configured acyclic enones are comparatively "easy" substrates that can be converted to enantiomerically highly enriched epoxides by all three methods. Currently, chiral ketones/dioxiranes constitute the only catalyst system that enables asymmetric and metal-free epoxidation of (*E*)-enoates. There seems to be no metal-free method for efficient asymmetric epoxidation of achiral (*Z*)-enones. Exocyclic (*E*)-enones have been epoxidized with excellent ee using either phase-transfer catalysis or polyamino acids. In contrast, generation of enantiopure epoxides from "normal" endocyclic

enones still poses considerable problems. In the special case of benzoquinone monoacetals, enantiomeric excesses > 90% have been achieved by phase-transfer catalysis, and some naphthoquinones yield enantiomerically highly enriched epoxides in the presence of bovine serum albumin (BSA). Further improvement is desirable for the organocatalytic asymmetric epoxidation of "simple" (*Z*)-cyclic enones such as cyclohexenones, cyclopentenones, etc.

10.3 Sulfoxidation of Thioethers

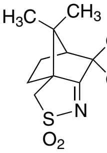
As mentioned in Section 10.1, the imine-oxaziridine couple **E**–**F** has been used for asymmetric sulfoxidation of prochiral thioethers (Scheme 10.16). Several highly enantioselective but stoichiometric asymmetric sulfoxidations – using isolated oxaziridines – have been described in the literature [121–124]. In contrast, few sulfoxidations involving the *in-situ* formation of the chiral oxidant **F** have been reported. Page et al. found that camphor-derived *N*-sulfonyl imines are active and highly selective mediators of this reaction [125, 126]. Unfortunately, to obtain satisfactory enantioselectivity they must be employed in stoichiometric amounts. Examples in which enantiomeric excesses of product sulfoxides greater than ca. 70% have been achieved are summarized in Table 10.11. It should be noted that the substrate spectrum encompasses pyridyl-substituted thioethers. In metal-catalyzed oxidations substrates with metal-binding substructures (for example, a pyridine moiety) tend to induce either catalyst deactivation and/or low enantioselectivity, because of displacement of the chiral ligand.



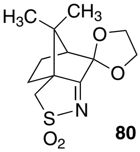
Scheme 10.16

In the *N*-sulfonyl imine-catalyzed sulfoxidation, aqueous hydrogen peroxide serves as the final oxidizing agent, which is clearly of practical advantage. In principle it can be assumed that either an oxaziridine (**F**, Scheme 10.17) or a hydroperoxy hemiaminal (**H**, Scheme 10.17) can result as the active species from the reaction of the *N*-sulfonyl imine **E** with hydrogen peroxide (Scheme 10.17). For imine **79** the idea of an intermediate oxaziridine is supported by the experimental finding that oxidation by the isolated oxaziridine and in the catalytic reaction (using **79** and

Tab. 10.11

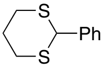
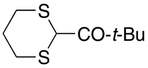
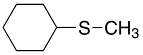
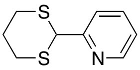


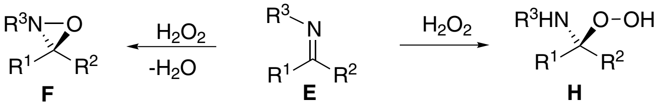
79



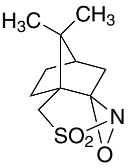
80

Typical sulfoxidation conditions: thioether (1 eq.), N-sulfonylimine (1 eq.), aqueous H_2O_2 (4 eq.), DBU (4 eq.) in CH_2Cl_2, −15 °C

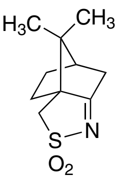
Catalyst	*Substrate*	*Yield of sulfoxide (%)*	*ee of sulfoxide (%)*	*Configuration of sulfoxide*
79	*t*-Bu–S–CH_3	quant.	86	*S*
80		quant.	82	*S*
79		quant.	98	*S*
80		quant.	94	*S*
79		46	78	*S*
80		74	68	*S*
80		quant.	68	(+)
79		69	98	*S*



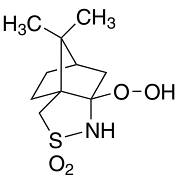
F E H



82



81

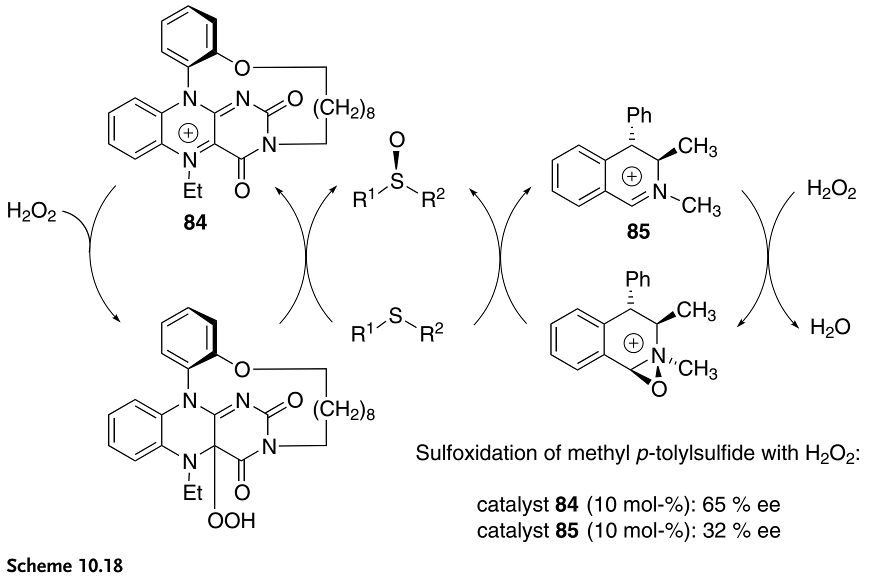


83

Scheme 10.17

hydrogen peroxide) give comparable yields and ee and the same sense of configuration. For the "basic" camphor *N*-sulfonyl imine **81**, however, it was shown that oxidation of methyl *t*-butyl sulfide by the isolated oxaziridine **82** gave the sulfoxide of *opposite* configuration compared with that obtained from catalytic sulfoxidation performed with hydrogen peroxide in the presence of the imine **81** (Scheme 10.17) [127–129]. This result clearly indicates that different oxygen-transferring intermediates are operating in this reaction, the most likely being the hydroperoxy amine **83** (Scheme 10.17) [130]. The intermediacy of a hydroperoxy amine in the catalytic cycle can by now be generally assumed for *N*-sulfonyl imine-mediated sulfoxidations with hydrogen peroxide [129].

It should finally be mentioned that asymmetric and metal-free sulfoxidation can also be achieved by use of flavinium (**84**) [131] or simpler chiral iminium cations (**85**) as catalysts [132] (Scheme 10.18). For the axially chiral flavinophane **84** enantiomeric excesses up to 65% were reported by Toda et al. (for methyl *p*-tolyl sulfide as substrate), at typical catalyst loadings of ca. 10 mol% (relative to the thioether). The same substrate gave the sulfoxide with 32% ee when the iminium cation **85** was used [132].



Scheme 10.18

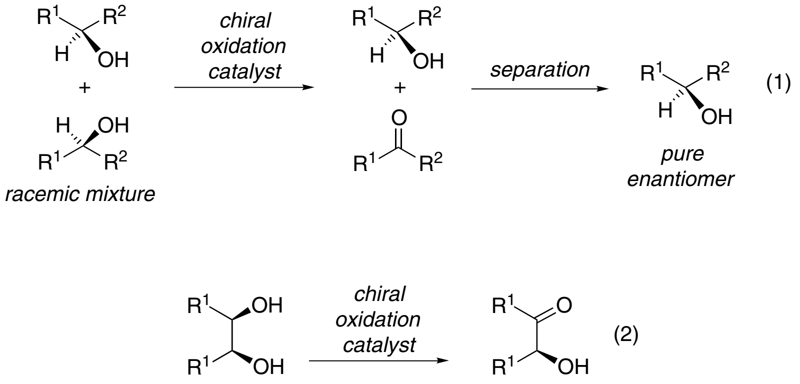
An alternative method for asymmetric and metal-free sulfoxidation was explored by Kita et al. [133]. In their approach, iodosylbenzene ($Ph\text{-}IO_2$) was used as oxidant in reversed micelles formed by cetyltrimethylammonium bromide (CTAB) in toluene. From the numerous chiral inductors tested, tartaric acid derivatives proved best. In the presence of 10 mol% bis(2-methoxybenzoyl)tartaric acid, methyl (4-nitrophenyl)sulfide was converted into the sulfoxide in 91% yield and with 72% enantiomeric excess [133].

Conclusions

Few examples of highly enantioselective (up to 98%) metal-free sulfoxidations have yet been reported. The catalysts that have proven most efficient in this respect are camphor-derived *N*-sulfonyl imines. It is advantageous that aqueous hydrogen peroxide can be used as the final oxidizing agent, but catalyst loadings are still high – up to 100 mol%. Clearly, the significant background reactivity of thioethers toward hydrogen peroxide make use of highly reactive catalysts essential if practically useful enantiomeric excesses are to be achieved at reasonably low catalyst loadings. The combination of micellar systems with chiral inductors is an interesting alternative. Encouraging results were achieved with iodosylbenzene as oxidant (up to 72% ee) whereas hydrogen peroxide afforded much lower enantioselectivity.

10.4 Oxidation of Alcohols

Catalytic oxidation is a possible means of kinetic resolution of racemic mixtures of alcohols (Scheme 10.19, Eq. 1) or of desymmetrization of *meso*-diols (Scheme 10.19, Eq. 2).

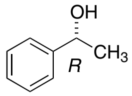
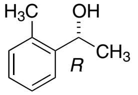
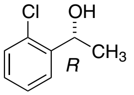
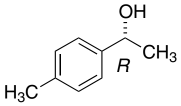
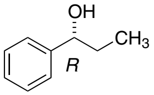
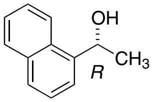
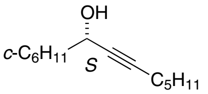
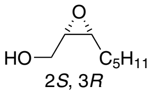


Scheme 10.19

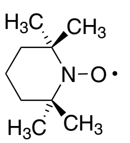
10.4.1 Kinetic Resolution of Racemic Alcohols

The oxidation of alcohols to carbonyl compounds with the stable nitroxyl radical TEMPO (**86**) as catalyst is a well-known preparative method [134, 135]. Hypochlorite or peracetic acid is usually used as the final oxidizing agent and ca. 1 mol% of catalyst **86** is used. In 1996 Rychnovsky et al. reported the synthesis of the chiral, binaphthyl-derived TEMPO analog **87** [136]. Results obtained by use of 0.5–1 mol% of catalyst **87** [136] are listed in Table 10.12. In these oxidation reactions 0.6–0.7 equiv. sodium hypochlorite were used as the final oxidizing agent (plus

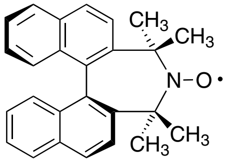
Tab. 10.12

mol-% 87	*Recovered alcohol*	*ee (%)*	*Conversion (%)*	*S*
0.5 1.0		81 98	69 87	5.0 7.1
1.0		73	58	6.8
1.0		89	70	6.0
1.0		64	58	5.1
1.0		57	59	3.9
0.5		57	56	4.5
0.5		41	66	2.2
0.5		19	58	1.5

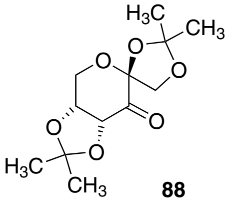
0.1 equiv. potassium bromide) in a two-phase system containing the substrate and catalyst **87** in dichloromethane at 0 °C. It is apparent from the table that the best selectivity factors (≥ 5) were obtained by use of 1-phenylethanol and its derivatives as substrates.



86

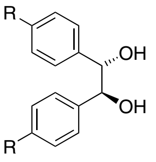
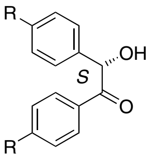
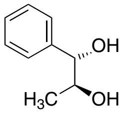
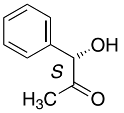
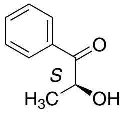


87



88

Tab. 10.13

Starting racemic diol	*Conversion (%)*	*Product hydroxy ketone*	*ee (%)*
	R = H 51 R = CH_3 12 R = F 31 R = Cl 11 R = Br 10 R = CN 6		65 61 69 70 74 75
	20		44
			69

Whereas the chiral TEMPO analog **87** was used to resolve racemic secondary alcohols, the D-fructose-derived ketone **88** [137] proved useful for oxidative resolution of racemic diols (Table 10.13) [138, 139]. Persulfate in the form of Oxone, Curox, etc., served as the final oxidizing agent, and the dioxirane generated from the ketone **88** is the chiral active species. Because of the relatively low conversions (except for unsubstituted dihydrobenzoin) at which the ee stated were achieved, the method currently seems to be of less practical value. Furthermore, typically 3 equiv. ketone **88** had to be employed [138, 139].

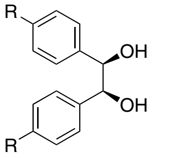
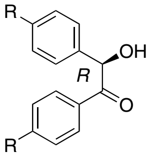
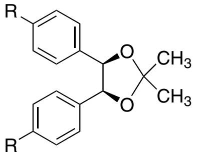
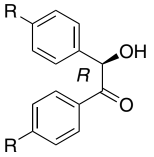
10.4.2
Desymmetrization of *meso* Diols

A series of meso-dihydrobenzoins was also subjected to oxidative desymmetrization. Three equivalents of the chiral ketone **88** again provided the chiral dioxirane as the active species [138, 139]. As shown in Table 10.14, enantiomeric excesses up to 60% were achieved. In addition to the meso diols themselves, acetonides also proved suitable substrates in two instances (Table 10.14).

Conclusions

The chiral TEMPO-derivative **87** has been shown to be an active catalyst for the oxidative kinetic resolution of 1-phenylethanol and derivatives. Catalyst loadings are in a practically very useful range (0.5–1 mol%) and hypochlorite is an attractive oxidant. Clearly, a more readily accessible catalyst would be desirable. In this respect, the Shi ketone **88** is advantageous. It must, however, be used in large excess and

Tab. 10.14

Starting meso-diol	Conversion (%)		Product hydroxy ketone	ee (%)
	R = H	89		45
	R = OCH_3	95		24
	R = CH_3	92		30
	R = F	95		58
	R = Cl	56		54
	R = Br	61		58
	R = CN	≤5		60
	R = H	10		63
	R = CH_3	10		65

preparatively useful enantiomeric excesses were achieved in a rather limited number of instances only.

Finally, it should be noted that achiral dioxiranes can be used to generate chiral hydroxyketones from enantiomerically pure diols or acetals [140, 141].

References

1 T. Katsuki, V. S. Martin, *Org. React.* **1996**, *48*, 1–300.

2 T. Katsuki, in *Comprehensive Asymmetric Catalysis*, (E. N. Jacobsen, A. Pfaltz, H. Yamamoto, Eds.), Springer, Berlin (1999), pp. 621–648.

3 E. N. Jacobsen, M. H. Wu, in *Comprehensive Asymmetric Catalysis*, (E. N. Jacobsen, A. Pfaltz, H. Yamamoto, Eds.), Springer, Berlin (1999), pp. 649–678.

4 T. Katsuki, *Coord. Chem. Rev.* **1995**, *140*, 189–214.

5 P. A. Ganeshpure, W. Adam, *Synthesis* **1996**, 179–188.

6 For a general review of metal-free oxidation, including achiral and chiral catalysts, see: W. Adam, C. R. Saha-Möller, P. A. Ganeshpure, *Chem. Rev.* **2001**, *101*, 3499–3548.

7 R. Curci, M. Fiorentino, M. R. Serio, *J. Chem. Soc., Chem. Commun.* **1984**, 155–156.

8 R. Curci, L. D'Accolti, M. Fiorentino, A. Rosa, *Tetrahedron Lett.* **1995**, *36*, 5831–5834.

9 D. Yang, Y.-C. Yip, M.-W. Tang, M.-K. Wong, J.-H. Zheng, K.-K. Cheung, *J. Am. Chem. Soc.* **1996**, *118*, 491–492.

10 D. Yang, X.-C. Wang, M.-K. Wong, Y.-C. Yip, M.-W. Tang, *J. Am. Chem. Soc.* **1996**, *118*, 11311–11312.

11 D. Yang, M.-K. Wong, Y.-C. Yip, X.-C. Wang, M.-W. Tang, J.-H. Zheng, K.-K. Cheung, *J. Am. Chem. Soc.* **1998**, *120*, 5943–5952.

12 C. E. Song, Y. H. Kim, K. C. Lee, S.-G. Lee, B. W. Jin, *Tetrahedron: Asymmetry* **1997**, *8*, 2921–2926.

13 Y. H. Kim, K. C. Lee, D. Y. Chi, S.-G. Lee, C. E. Song, *Bull. Korean Chem. Soc.* **1999**, *20*, 831–834.

14 Y. Tu, Z.-X. Wang, Y. Shi, *J. Am. Chem. Soc.* **1996**, *118*, 9806–9807.

15 Z.-X. Wang, Y. Tu, M. Frohn, Y. Shi, *J. Org. Chem.* **1997**, *62*, 2328–2329.

16 (a) M. Frohn, Y. Shi, *Synthesis* **2000**, 1979–2000; (b) M. Frohn, Y. Shi, *Org. Synth.* **2003**, *80*, 1–12.

17 M. Frohn, M. Dalkiewicz, Y. Tu, Z.-X. Wang, Y. Shi, *J. Org. Chem.* **1998**, *63*, 2948–2953.

18 Z.-X. Wang, G.-A. Cao, Y. Shi, *J. Org. Chem.* **1999**, *64*, 7646–7650.

19 G.-A. Cao, Z.-X. Wang, Y. Tu, Y. Shi, *Tetrahedron Lett.* **1998**, *39*, 4425–4428.

20 (a) Z. Xiong, E. J. Corey, *J. Am. Chem. Soc.* **2000**, *122*, 4831–4832; (b) Z. Xiong, E. J. Corey, *J. Am. Chem. Soc.* **2000**, *122*, 9328–9329.

21 (a) H. Tian, X. She, Y. Shi, *Org. Lett.* **2001**, *3*, 715–718; (b) H. Tian, X. She, H. Yu, L. Shu, Y. Shi, *J. Org. Chem.* **2002**, *67*, 2435–2446; (c) L. Shu, P. Wang, Y. Gan, Y. Shi, *Org. Lett.* **2003**, *5*, 293–296; (d) L. Shu, Y.-M. Shen, C. Burke, D. Goeddel, Y. Shi, *J. Org. Chem.* **2003**, *68*, 4963–4965.

22 (a) H. Tian, X. She, L. Shu, H. Yu, Y. Shi, *J. Am. Chem. Soc.* **2000**, *122*, 11551–11552; (b) H. Tian, X. She, J. Xu, Y. Shi, *Org. Lett.* **2001**, *3*, 1929–1931.

23 Z.-X. Wang, S. M. Miller, O. P. Anderson, Y. Shi, *J. Org. Chem.* **2001**, *66*, 521–530.

24 Z.-X. Wang, Y. Shi, *J. Org. Chem.* **1997**, *62*, 8622–8623.

25 Z.-X. Wang, S. M. Miller, O. P. Anderson, Y. Shi, *J. Org. Chem.* **1999**, *64*, 6443–6458.

26 W. Adam, C. R. Saha-Möller, C.-G. Zhao, *Tetrahedron: Asymmetry* **1999**, *10*, 2749–2755.

27 W. Adam, C.-G. Zhao, *Tetrahedron: Asymmetry* **1997**, *8*, 3995–3998.

28 D. Yang, G.-S. Jiao, Y.-C. Yip, T.-H. Lai, M.-K. Wong, *J. Org. Chem.* **2001**, *66*, 4619–4624.

29 M. Frohn, X. Zhou, J.-R. Zhang, Y. Tang, Y. Shi, *J. Am. Chem. Soc.* **1999**, *121*, 7718–7719.

30 (a) Y. Zhu, Y. Tu, H. Yu, Y. Shi, *Tetrahedron Lett.* **1998**, *39*, 7819–7822; (b) Y. Zhu, L. Shu, Y. Tu, Y. Shi, *J. Org. Chem.* **2001**, *66*, 1818–1826.

31 W. Adam, R. T. Fell, C. R. Saha-Möller, C.-G. Zhao, *Tetrahedron: Asymmetry* **1998**, *9*, 397–401.

32 A. Solladié-Cavallo, P. Lupatelli, L. Jierry, P. Bovicelli, F. Angeli, R. Antonioletti, A. Klein, *Tetrahedron Lett.* **2003**, *44*, 6523–6526.

33 A. Solladié-Cavallo, L. Bouérat, L. Jierry, *Eur. J. Org. Chem.* **2001**, 4557–4563.

34 (a) S. E. Denmark, Z. Wu, *Synlett* **1999**, 847–859; (b) S. E. Denmark, H. Matsuhashi, *J. Org. Chem.* **2002**, *67*, 3479–3486.

35 S. E. Denmark, Z. Wu, C. M. Crudden, H. Matsuhashi, *J. Org. Chem.* **1997**, *62*, 8288–8289.

36 A. Armstrong, B. R. Hayter, *Chem. Commun.* **1998**, 621–622.

37 (a) A. Armstrong, B. R. Hayter, W. O. Moss, J. R. Reeves, J. S. Wailes, *Tetrahedron: Asymmetry* **2000**, *11*, 2057–2061; (b) A. Armstrong, G. Ahmed, B. Dominguez-Fernandez, B. R. Hayter, J. S. Wailes, *J. Org. Chem.* **2002**, *67*, 8610–8617.

38 G. S. Lal, *J. Org. Chem.* **1993**, *58*, 2791–2796.

39 L. Shu, Y. Shi, *Tetrahedron Lett.* **1999**, *40*, 8721–8724.

40 L. Shu, Y. Shi, *Tetrahedron* **2001**, *57*, 5213–5218.

41 L. Bohé, G. Hanquet, M. Lusinchi, X. Lusinchi, *Tetrahedron Lett.* **1993**, *34*, 7271–7274.

42 L. Bohé, M. Lusinchi, X. Lusinchi, *Tetrahedron* **1999**, *55*, 141–145.

43 S. Minakata, A. Takemiya, K. Nakamura, I. Ryu, M. Komatsu, *Synlett* **2000**, 1810–1812.

44 P. C. B. Page, G. A. Rassias, D. Bethell, M. B. Schilling, *J. Org. Chem.* **1998**, *63*, 2774–2777.

45 P. C. B. Page, G. A. Rassias, D. Barros, A. Ardakani, B. Buckley, D. Bethell, T. A. D. Smith, A. M. Slawin, *J. Org. Chem.* **2001**, *66*, 6926–6931.

46 P. C. B. Page, G. A. Rassias, D. Barros, A. Ardakani, D. Bethell, E. Merifield, *Synlett* **2002**, 580–582.

47 M.-K. Wong, L.-M. Ho, Y.-S. Zheng, C.-Y. Ho, D. Yang, *Org. Lett.* **2001**, *3*, 2587–2590.

48 (a) V. K. Aggarwal, M. F. Wang, *J. Chem. Soc., Chem. Commun.* **1996**, 191–192; (b) P. C. B. Page, B. R. Buckley, A. J. Blacker, *Org. Lett.* **2004**, *6*, 1543–1546.

49 M. F. A. Adamo, V. K. Aggarwal, M. A. Sage, *J. Am. Chem. Soc.* **2000**, *122*, 8317–8318.

50 M. F. A. Adamo, V. K. Aggarwal, M. A. Sage, *J. Am. Chem. Soc.* **2002**, *124*, 11223.

51 V. K. Aggarwal, C. Lopin, F. Sandrinelli, *J. Am. Chem. Soc.* **2003**, *125*, 7596–7601.

52 For general reviews of the asymmetric epoxidation of electron-deficient olefins, see Refs. 53–55.

53 V. K. Aggarwal in *Comprehensive Asymmetric Catalysis* (E. N. Jacobsen, A. Pfaltz, H. Yamamoto, Eds.), Springer, Berlin (1999), pp. 679–698.

54 M. J. Porter, J. Skidmore, *J. Chem. Soc., Chem. Commun.* **2000**, 1215–1225.

55 L. Pu, *Tetrahedron: Asymmetry* **1998**, *9*, 1457–1477.

56 D. Enders, J. Zhu, L. Kramps, *Liebigs Ann./Receuil* **1997**, 1101–1113.

57 D. Enders, J. Zhu, G. Raabe, *Angew. Chem.* **1996**, *108*, 1827–1829; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1725–1728.

58 O. Jacques, S. J. Richards, R. F. W. Jackson, *J. Chem. Soc., Chem. Commun.* **2001**, 2712–2713.

59 C. L. Elston, R. F. W. Jackson, S. J. F. Macdonald, P. J. Murray, *Angew. Chem.* **1997**, *109*, 379–381; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 410–412.

60 T. Nemoto, T. Ohshima, M. Shibasaki, *J. Am. Chem. Soc.* **2001**, *123*, 9474–9475.

61 T. Nemoto, T. Ohshima, K. Yamaguchi, M. Shibasaki, *J. Am. Chem. Soc.* **2001**, *123*, 2725–2732.

62 (a) Z. X. Wang, Y. Shi, *J. Org. Chem.* **1997**, *62*, 8622–8623; (b) Z.-X. Wang, S. M. Miller, O. P. Anderson, Y. Shi, *J. Org. Chem.* **1999**, *64*, 6443–6458.

63 X.-Y. Wu, X. She, Y. Shi, *J. Am. Chem. Soc.* **2002**, *124*, 8792–8793.

64 A. Armstrong, B. R. Hayter, *Chem. Commun.* **1998**, 621–622.

65 (a) A. Solladié-Cavallo, L. Bouérat, L. Jierry, *Eur. J. Org. Chem.* **2001**, 4557–4560; (b) A. Solladié-Cavallo, L. Bouérat, *Org. Lett.* **2000**, *2*, 3531–3534; (c) R. Imashiro, M. Seki, *J. Org. Chem.* **2004**, *69*, 4216–4226.

66 (a) S. Juliá, J. Guixer, J. Masana, J. Rocas, S. Colonna, R. Annuziata, H. Molinari, *J. Chem. Soc., Perkin Trans. 1* **1982**, 1317–1324; (b) S. Juliá, J. Masana, J. C. Vega, *Angew. Chem.* **1980**, *92*, 968–969; *Angew. Chem. Int. Ed. Engl.* **1980**, *19*, 929–931.

67 P. A. Bentley, W. Kroutil, J. A. Littlechild, S. M. Roberts, *Chirality* **1997**, *9*, 198–202.

68 M. E. Lasterra-Sánchez, U. Felfer, P. Mayon, S. M. Roberts, S. R. Thornton, C. J. Todd, *J. Chem. Soc., Perkin Trans. 1*, **1995**, 343–348.

69 W. Kroutil, P. Mayon, M. E. Lasterra-Sánchez, S. J. Maddrell, S. M. Roberts, S. R. Thornton, C. J. Todd, M. Tüter, *J. Chem. Soc., Chem. Commun.* **1996**, 845–846.

70 J. R. Flisak, K. J. Gombatz, M. M. Holmes, A. A. Jarmas, I. Lantos, W. L. Mendelson, V. J. Novack, J. J. Remich, L. Snyder, *J. Org. Chem.* **1993**, *58*, 6247–6254.

71 M. E. Lasterra-Sanchéz, S. M. Roberts, *J. Chem. Soc., Perkin Trans. 1* **1995**, 1467–1468.

72 J. R. Falck, R. K. Bhatt, K. M. Reddy, J. H. Ye, *Synlett* **1997**, 481–482.

73 B. M. Adger, J. V. Barkley, S. Bergeron, M. W. Cappi, B. E. Flowerdew, M. P. Jackson, R. McCague, T. C. Nugent, S. M. Roberts, *J. Chem. Soc., Perkin Trans 1* **1997**, 3501–3507.

74 P. A. Bentley, S. Bergeron, M. W. Cappi, D. E. Hibbs, M. B. Hursthouse, T. C. Nugent, R. Pulido, S. M. Roberts, L. E. Wu, *J. Chem. Soc., Chem. Commun.* **1997**, 739–740.

75 J. V. Allen, K.-H. Drauz, R. W. Flood, S. M. Roberts, J. Skidmore, *Tetrahedron Lett.* **1999**, *40*, 5417–5420.

76 J. V. Allen, S. Bergeron, M. J. Griffith, S. Mukherjee,

S. M. Roberts, N. M. Williamson, L. E. Wu, *J. Chem. Soc., Perkin Trans. 1*, **1998**, 3171–3180.
77 A. Dhanda, K.-H. Drauz, T. P. Geller, S. M. Roberts, *Chirality* **2000**, *12*, 313–317.
78 S. Itsuno, M. Sakakura, K. Ito, *J. Org. Chem.* **1990**, *55*, 6047–6049.
79 T. Geller, S. M. Roberts, *J. Chem. Soc., Perkin Trans. 1* **1999**, 1397–1398.
80 L. Carde, H. Davies, T. P. Geller, S. M. Roberts, *Tetrahedron Lett.* **1999**, *40*, 5421–5424.
81 W.-P. Chen, A. L. Egar, M. B. Hursthouse, K. M. A. Malik, J. E. Mathews, S. M. Roberts, *Tetrahedron Lett.* **1998**, *39*, 8495–8498.
82 J. V. Allen, M. W. Cappi, P. D. Kary, S. M. Roberts, N. M. Williamson, L. E. Wu, *J. Chem. Soc., Perkin Trans. 1* **1997**, 3297–3298.
83 W. Kroutil, M. E. Lasterra-Sánchez, S. J. Maddrell, P. Mayon, P. Morgan, S. M. Roberts, S. R. Thornton, C. J. Todd, M. Tüter, *J. Chem. Soc., Perkin Trans. 1* **1996**, 2837–2844.
84 P. A. Bentley, J. F. Bickley, S. M. Roberts, A. Steiner, *Tetrahedron Lett.* **2001**, *42*, 3741–3743.
85 P. W. Baures, D. S. Eggleston, J. R. Flisak, K. Gombatz, I. Lantos, W. Mendelson, J. J. Remich, *Tetrahedron Lett.* **1990**, *31*, 6501–6504.
86 R. J. J. Nel, P. S. van Heerden, H. van Rensburg, D. Ferreira, *Tetrahedron Lett.* **1998**, *39*, 5623–5626.
87 H. van Rensburg, P. S. van Heerden, B. C. B. Bezuidenhoudt, D. Ferreira, *Tetrahedron* **1997**, *53*, 14141–14152.
88 A. T. Gillmore, S. M. Roberts, M. B. Hursthouse, K. M. A. Malik, *Tetrahedron Lett.* **1998**, *39*, 3315–3318.
89 J. A. Bickley, A. T. Gillmore, S. M. Roberts, J. Skidmore, A. Steiner, *J. Chem. Soc., Perkin Trans. 1* **2001**, 1109–1115.
90 P. C. Ray, S. M. Roberts, *Tetrahedron Lett.* **1999**, *40*, 1779–1782.
91 R. W. Flood, T. P. Geller, S. A. Petty, S. M. Roberts, J. Skidmore, M. Volk, *Org. Lett.* **2001**, *3*, 683–686.
92 S. B. Tsogoeva, J. Wöltinger, C. Jost, D. Reichert, A. Kühnle, H.-P. Krimmer, K. Drauz, *Synlett* **2002**, 707–710.
93 P. A. Bentley, M. W. Cappi, R. W. Flood, S. M. Roberts, J. A. Smith, *Tetrahedron Lett.* **1998**, *39*, 9297–9300.
94 R. Takagi, A. Shiraki, T. Manabe, S. Kojima, K. Ohkata, *Chem. Lett.* **2000**, 366–367.
95 A. Berkessel, N. Gasch, K. Glaubitz, C. Koch, *Org. Lett.* **2001**, *3*, 3839–3842.
96 S. Colonna, A. Manfredi, *Tetrahedron Lett.* **1986**, *27*, 387–390.
97 S. Colonna, A. Manfredi, R. Annunziata, M. Spadoni, *Tetrahedron* **1987**, *43*, 2157–2164.
98 S. Colonna, A. Manfredi, M. Spadoni, *Tetrahedron Lett.* **1987**, *28*, 1577–1580.
99 S. Colonna, N. Gaggero, A. Manfredi, M. Spadoni, L. Casella, G. Carrea, P. Pasta, *Tetrahedron* **1988**, *44*, 5169–5178.
100 A. Nelson, *Angew. Chem.* **1999**, *111*, 1685–1687; *Angew. Chem. Int. Ed.* **1999**, *38*, 1583–1585.
101 R. Helder, J. C. Hummelen, R. W. P. M. Laane, J. S. Wiering, H. Wynberg, *Tetrahedron Lett.* **1976**, 1831–1834.
102 J. C. Hummelen, H. Wynberg, *Tetrahedron Lett.* **1978**, 1089–1092.
103 H. Wynberg, B. Greijdanus, *J. Chem. Soc., Chem. Commun.* **1978**, 427–428.
104 H. Pluim, H. Wynberg, *J. Org. Chem.* **1980**, *45*, 2498–2502.
105 H. Wynberg, B. Marsman, *J. Org. Chem.* **1980**, *45*, 158–161.
106 Y. Harigaya, H. Yamaguchi, M. Onda, *Heterocycles* **1981**, *15*, 183–185.
107 N. Baba, J. Oda, M. Kawaguchi, *Agric. Biol. Chem.* **1986**, *50*, 3113–3117.
108 N. Baba, S. Kawahara, M. Hamada, J. Oda, *Bull. Inst. Chem. Res. Kyoto Univ.* **1987**, *65*, 144–146.
109 N. Baba, J. Oda, S. Kawahara, M. Hamada, *Bull. Inst. Chem. Res. Kyoto Univ.* **1989**, *67*, 121–127.
110 G. Macdonald, L. Alcaraz, N. J. Lewis, R. J. K. Taylor, *Tetrahedron Lett.* **1998**, *39*, 5433–5436.

111 L. Alcaraz, G. Macdonald, J. P. Ragot, N. Lewis, R. J. K. Taylor, *J. Org. Chem.* **1998**, *63*, 3526–3527.

112 A. G. M. Barrett, F. Blaney, A. D. Campbell, D. Hamprecht, T. Meyer, A. J. P. White, D. Witty, D. J. Williams, *J. Org. Chem.* **2002**, *67*, 2735–2750.

113 W. Adam, P. B. Rao, H.-G. Degen, C. R. Saha-Möller, *Tetrahedron: Asymmetry* **2001**, *12*, 121–125.

114 W. Adam, P. B. Rao, H.-G. Degen, A. Levai, T. Patonay, C. R. Saha-Möller, *J. Org. Chem.* **2002**, *67*, 259–264.

115 B. Lygo, D. C. M. To, *Tetrahedron Lett.* **2001**, *42*, 1343–1346.

116 B. Lygo, P. G. Wainwright, *Tetrahedron Lett.* **1998**, *39*, 1599–1602.

117 B. Lygo, P. G. Wainwright, *Tetrahedron* **1999**, *55*, 6289–6300.

118 E. J. Corey, F.-Y. Zhang, *Org. Lett.* **1999**, *1*, 1287–1290.

119 S. Arai, H. Tsuge, T. Shiori, *Tetrahedron Lett.* **1998**, *39*, 7563–7566.

120 (a) S. Arai, M. Oku, M. Miura, T. Shiori, *Synlett* **1998**, 1201–1202; (b) S. Arai, H. Tsuge, M. Oku, M. Miura, T. Shiori, *Tetrahedron* **2002**, *58*, 1623–1630; (c) T. Ooi, D. Ohara, M. Tamura, K. Marvoka, *J. Am. Chem. Soc.* **2004**, *126*, 6844–6845.

121 F. A. Davis, R. T. Reddy, W. Han, R. E. Reddy, *Pure Appl. Chem.* **1993**, *65*, 633–640.

122 F. A. Davis, B.-C. Chen, *Chem. Rev.* **1992**, *92*, 919–934.

123 J. C. Towson, M. C. Weismiller, G. S. Lal, A. C. Sheppard, F. A. Davis, *Org. Synth.* **1990**, *69*, 158–168.

124 C. Bolm, K. Muniz, J. P. Hildebrand in *Comprehensive Asymmetric Catalysis* (E. N. Jacobsen, A. Pfaltz, H. Yamamoto, Eds.), Springer, Berlin (1999), pp. 697–712.

125 P. C. B. Page, J. P. Heer, D. Bethell, B. A. Lund, *Phosphorous, Sulfur, Silicon* **1999**, *153/154*, 247–258.

126 D. Bethell, P. C. B. Page, H. Vahedi, *J. Org. Chem.* **2000**, *65*, 6756–6760.

127 P. C. B. Page, J. P. Heer, D. Bethell, E. W. Collington, D. M. Andrews, *Tetrahedron: Asymmetry* **1995**, *6*, 2911–2914.

128 P. C. B. Page, J. P. Heer, D. Bethell, E. W. Collington, D. M. Andrews, *Tetrahedron Lett.* **1994**, *35*, 9629–9632.

129 P. C. B. Page, J. P. Heer, D. Bethell, E. W. Collington, D. M. Andrews, *Synlett* **1995**, 773–775.

130 Whereas several X-ray structural analyses prove the endo orientation of the oxygen atom of the oxaziridine ring, the assumption of an exo oriented hydroperoxy group in **83** is based solely on the opposite sense of asymmetric induction observed for **82** and **83**.

131 S. Shinkai, T. Yamaguchi, O. Manabe, F. Toda, *J. Chem. Soc., Chem. Commun.* **1988**, 1399–1401.

132 L. Bohé, G. Hanquet, M. Lusinchi, X. Lusinchi, *Tetrahedron Lett.* **1993**, *34*, 7271–7274.

133 H. Tohma, S. Takizawa, H. Watanabe, Y. Fukuoaka, T. Maegawa, Y. Kita, *J. Org. Chem.* **1999**, *64*, 3519–3523.

134 P. L. Anelli, F. Montanari, S. Quici, *Org. Synth.* **1990**, *69*, 212–219.

135 P. L. Anelli, S. Banfi, F. Montanari, S. Quici, *J. Org. Chem.* **1989**, *54*, 2970–2972.

136 (a) S. D. Rychnovsky, T. L. McLernon, H. Rajapakse, *J. Org. Chem.* **1996**, *61*, 1194–1195; (b) For a review on the selective oxidation of secondary alcohols, see: J. B. Arterburn, *Tetrahedron* **2001**, *57*, 9765–9788.

137 M. Frohn, Y. Shi, *Synthesis* **2000**, 1979–2000.

138 W. Adam, C. R. Saha-Möller, C.-G. Zhao, *Tetrahedron: Asymmetry* **1998**, *9*, 4117–4122.

139 W. Adam, C. R. Saha-Möller, C.-G. Zhao, *J. Org. Chem.* **1999**, *64*, 7492–7497.

140 L. D'Accolti, A. Detomaso, C. Fusco, A. Rosa, R. Curci, *J. Org. Chem.* **1993**, *58*, 3600–3601.

141 R. Curci, L. D'Accolti, A. Dinoi, C. Fusco, A. Rosa, *Tetrahedron Lett.* **1996**, *37*, 115–118.

11
Reduction of Carbonyl Compounds

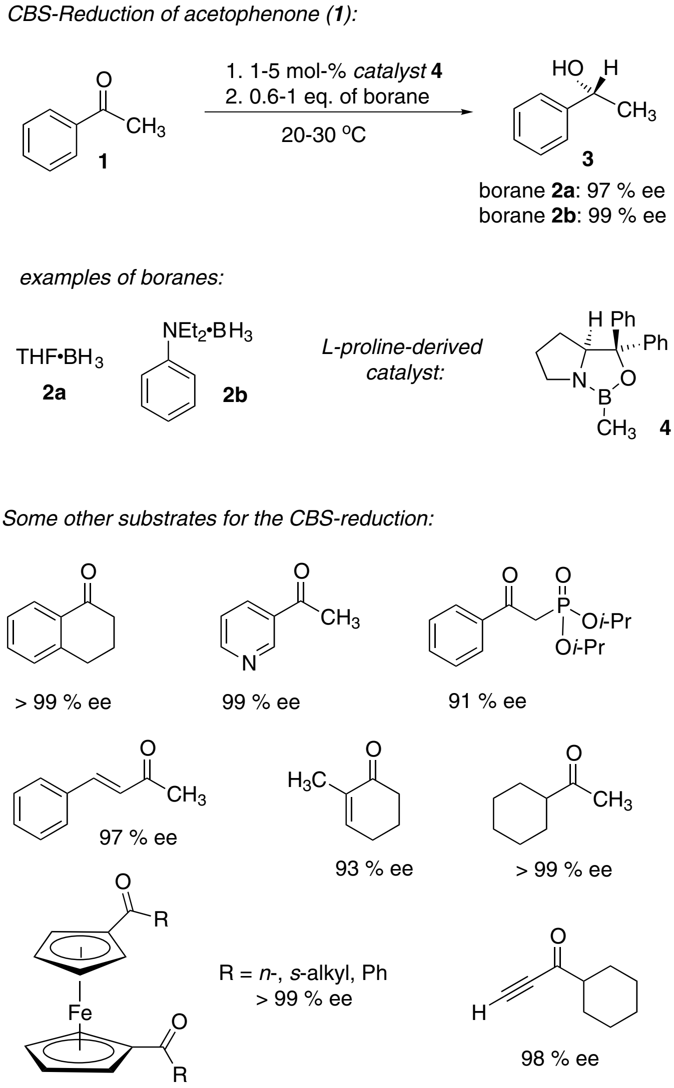
Organocatalytic asymmetric carbonyl reductions have been achieved with boranes in the presence of oxazaborolidine and phosphorus-based catalysts (Section 11.1), with borohydride reagents in the presence of phase-transfer catalysts (Section 11.2), and with hydrosilanes in the presence of chiral nucleophilic activators (Section 11.3).

11.1
Borane Reduction Catalyzed by Oxazaborolidines and Phosphorus-based Catalysts

Probably the most frequently applied catalytic metal-free and highly enantioselective reduction of carbonyl compounds is the oxazaborolidine-catalyzed borane reduction (the Corey–Bakshi–Shibata (CBS) method) [1–8]. In this approach, which is based on initial work by Itsuno et al. [1, 6–8], oxazaborolidines serve as the catalysts. These latter materials are derived from readily available amino alcohols; the most frequently used is probably the proline-derived bicyclic compound **4**. The CBS method has been successfully applied to all types of ketones, for example diaryl, dialkyl, and aryl alkyl ketones, haloalkyl ketones, transition metal π-complexes of aryl alkyl ketones, cyclic and open-chain enones, etc. [1–8]. Scheme 11.1 shows the explicit example of acetophenone (**1**) which can be reduced with boranes such as $BH_3 \cdot THF$ (**2a**), $BH_3 \cdot Me_2S$, catechol borane, or the borane–diethylaniline complex (**2b**) to give 1-phenylethanol **3** in very good yields and almost perfect enantiomeric excess.

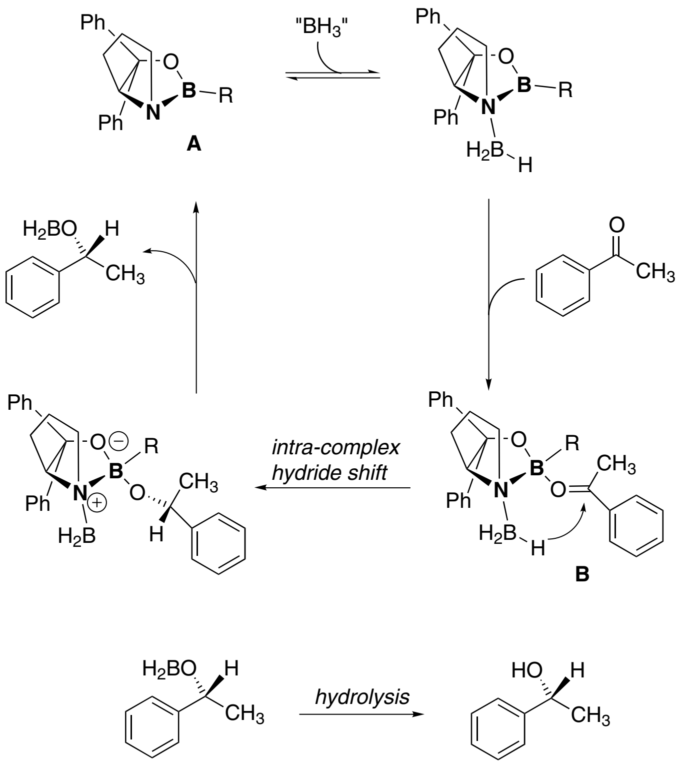
Scheme 11.1 also summarizes other impressive examples of the performance of the CBS method [1–8]. Several excellent reviews on the CBS method have appeared recently [1, 2], and no detailed discussion of the development of the process or substrate scope shall be presented in this review. Please note, however, that the oxazaborolidine-catalyzed borane reduction of ketones is a prime example of bifunctional catalysis [2, 9] – as shown in Scheme 11.2, the current mechanistic picture involves simultaneous binding of both the ketone and the borane to the Lewis-acidic (boron) and Lewis-basic (nitrogen) sites of the catalyst **A**. In the resulting ternary complex **B**, the reaction partners are synergistically activated toward hydride transfer.

Asymmetric Organocatalysis. Albrecht Berkessel and Harald Gröger
Copyright © 2005 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim
ISBN: 3-527-30517-3



Scheme 11.1

Related catalysts for asymmetric borane reduction of ketones are open chain and cyclic phosphoric amides, in the oxidation state +3 or +5 (Scheme 11.3) [10, 11]. Early examples are the phosphonamides and phosphinamides **5a** and **5b** of Wills et al. [12] and the oxazaphospholidine–borane complex **6a** of Buono et al. [13]. In the presence of 2–10 mol% catalysts **5a**,**b**, ω-chloroacetophenone was reduced by BH_3•SMe_2 with 35–46% ee [12]. For catalyst **6a** a remarkable 92% ee was reported for the catalytic reduction of methyl *iso*-butyl ketone and 75% ee for acetophenone

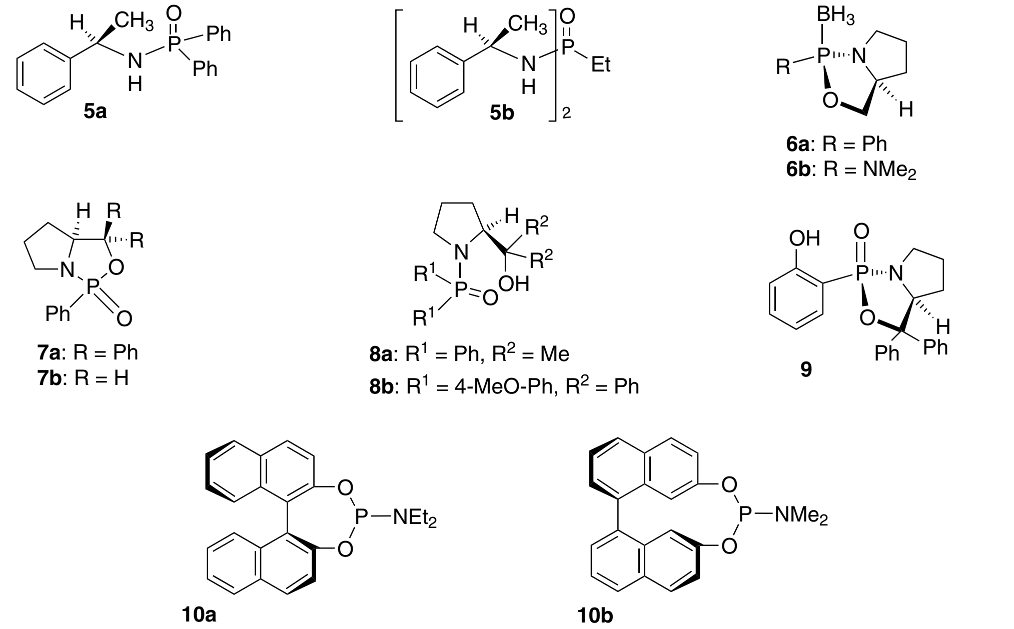


Scheme 11.2

(71% ee with **6b**) [13]. Martens and Peper tested several cyclic phosphonamides and identified the proline derivatives **7** as the most enantioselective catalysts. In the presence of as little as 1 mol% **7a**, ω-chloroacetophenone was reduced by BH_3•THF with 96% ee [14]. Under similar conditions the related catalyst **7b** of Buono et al. afforded 94% ee [15]. Mechanistically, it is believed that for oxygenated phosphorus(V) compounds the borane molecule binds to the oxygen atom and renders the phosphorus atom sufficiently electrophilic to bind the ketone substrate. Overall, a ternary complex analogous to **B**, Scheme 11.2, is formed [16c]. Wills et al. introduced hydroxy phosphoric amides such as **8a** and **8b** (Scheme 11.3) [16] and Brunel, Buono, et al. prepared (*o*-hydroxyaryl)oxazaphospholidine oxides such as **9** which afforded 84% ee in the reduction of ω-chloroacetophenone [17]. With the hydroxylated catalysts it is believed that a boronic ester, formed initially from the catalyst and the borane, acts as the electrophilic binding site for the substrate ketone, whereas the second, "reducing" borane molecule is coordinated to the oxygen atom of the P=O bond [16c].

The binaphthyl-derived phosphoramidites **10a** and **10b** have been used as cata-

Phosphoric amide catalysts for the borane reduction of ketones:



Some ketone substrates, catalysts and ees achieved:

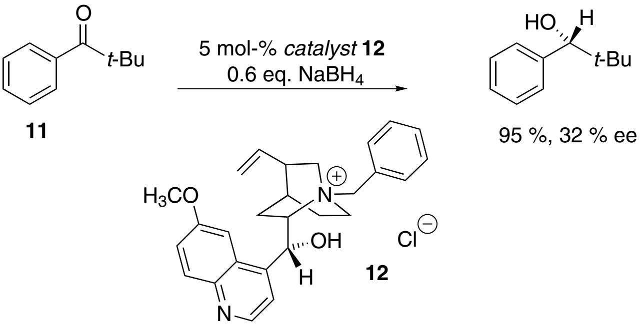
7a: 96 % ee (ref. 14) **8a**: 92 % ee (refs. 16a,c) **8b**: 94 % ee (ref. 16b) **9**: 84 % ee (ref. 17)	**6a**: 75 % ee (ref. 13a,b) **6b**: 71 % ee (ref. 13a) **8a**: 62 % ee (refs. 16a,c) **8b**: 88 % ee (ref. 16b) **10a**: 98 % ee (ref. 18) **10b**: 96 % ee (ref. 19)	**8b**: 90 % ee (ref. 16b)	**8b**: 90 % ee (ref. 16b)

Scheme 11.3

lysts in the asymmetric borane reduction of acetophenone by Tang et al. and Müller et al., respectively (Scheme 11.3). With THF•BH_3 as reducing agent, 6 mol% of the catalyst **10a** afforded 1-phenylethanol in ca. 95% yield and with ≥98% ee [18]. Similarly, 5 mol% **10b** gave almost quantitative yield and 96% ee [19].

11.2
Borohydride and Hydrosilane Reduction in the Presence of Phase-transfer Catalysts

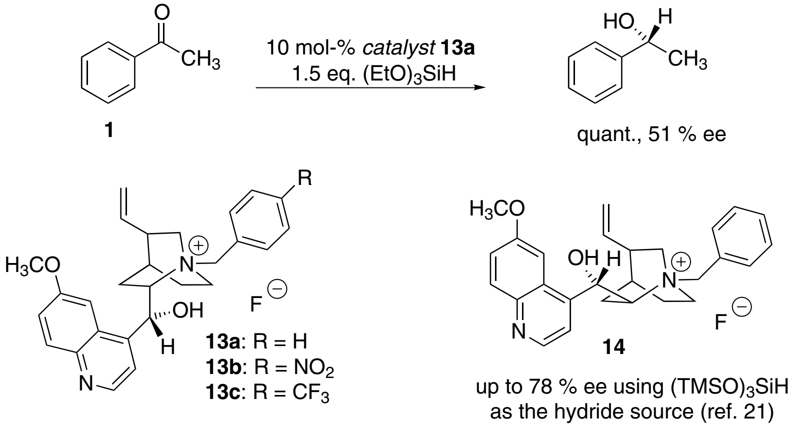
Compared with boranes, borohydrides are inexpensive and easy to handle. As early as 1978 Colonna and Fornasier reported that aryl alkyl ketones such as acetophenone can be reduced asymmetrically by sodium borohydride by use of an aqueous–organic two-phase system and chiral phase transfer catalysts [20]. In this study, the best enantiomeric excess (32%) was achieved when pivalophenone (**11**) was reduced in the presence of 5 mol% benzylquininium chloride (**12**) (Scheme 11.4) [20]. Other chiral phase-transfer catalysts, for example ephedrinium salts, proved less effective.



Scheme 11.4

Almost twenty years later, Lawrence et al. reported that benzylquininium fluoride **13a**, prepared from commercially available **12** by ion exchange, is an active and selective catalyst in the reduction of acetophenone (**1**) with triethoxysilane (51% ee; Scheme 11.5) [21].

The enantioselectivity achieved was highly dependent on the substituent present on the quaternary nitrogen atom of the quinine nucleus. For example, the 4-nitrobenzylammonium salt **13b** afforded a slightly increased ee (53%), whereas the 4-CF_3-substituted catalyst **13c** gave an almost racemic product (Scheme 11.5) [21]. When the pseudo-enantiomeric quinidine salt **14** was used the enantiomeric phenylethanol was obtained with slightly higher ee (62%). Further studies on the range of substrates and catalysts revealed that the aryl substituent in the substrate ketone is crucial for good enantioselection, and that increasing the steric bulk of the alkyl substituent improves the ee (65% for both phenyl ethyl and phenyl *iso*-propyl ketone). Polymethylhydrosiloxane (PMHS), an inexpensive and readily available hydrosilane, is a very active reducing agent under the reaction conditions studied, but ee are low. On the other hand, tris(trimethlysiloxy)silane gave best enantioselectivity (78% ee in the reduction of acetophenone using **14** as the catalyst). The authors also noted that *N*-benzylquininium *hydroxide* afforded almost the same



Scheme 11.5

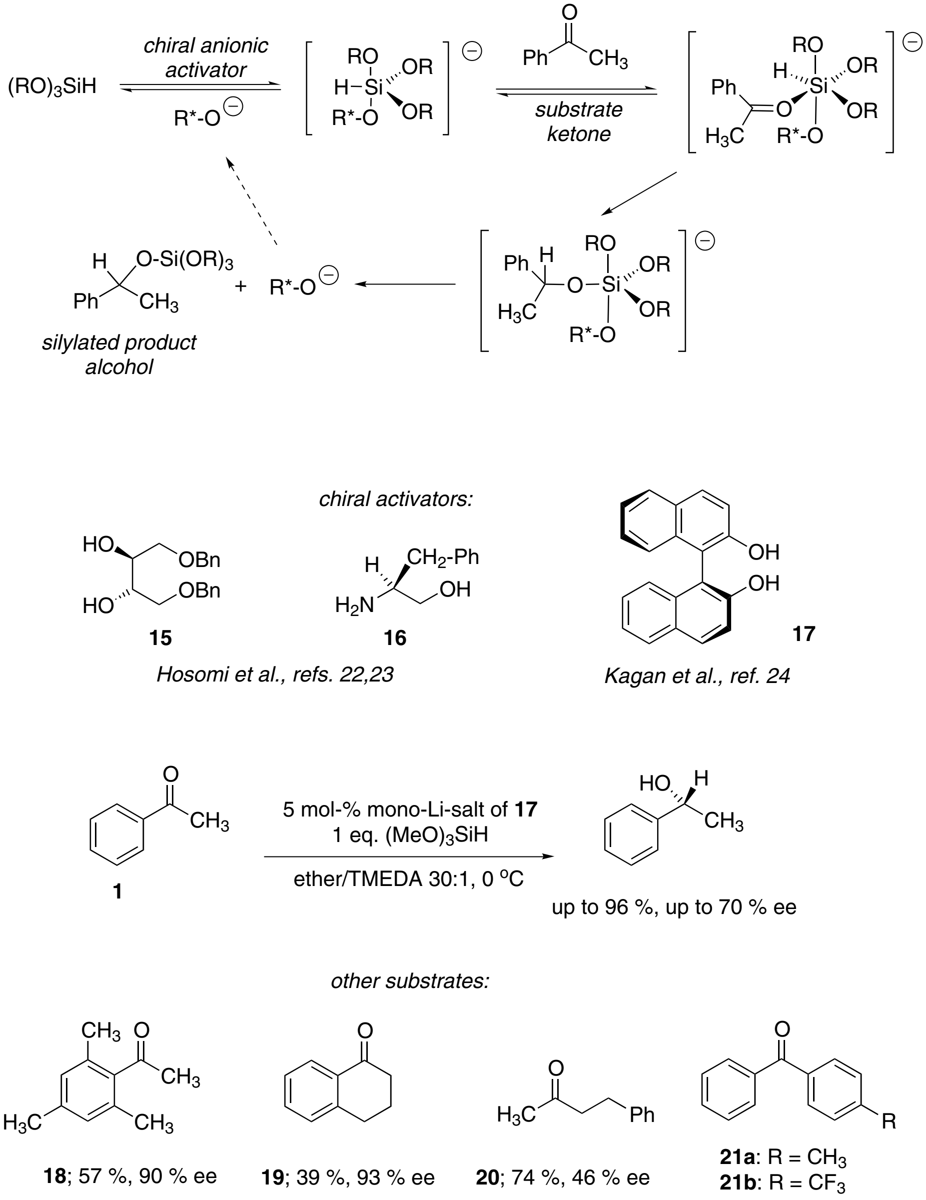
enantioselectivity as the fluoride **13a**. This result is interesting preparatively, but throws some doubt on the assumption that a hypervalent fluoride–alkoxide hydrosilicate anion is the active reducing agent [21].

11.3
Reduction with Hydrosilanes in the Presence of Chiral Nucleophilic Activators

In the phase-transfer processes discussed in Section 11.2 it is assumed that the anionic hydride source, i.e. borohydride or a hypervalent hydrosilicate, forms an ion-pair with the chiral cationic phase-transfer catalyst. As a consequence, hydride transfer becomes enantioselective. An alternative is that the nucleophilic activator needed to effect hydride transfer from a hydrosilane can act as the chiral inducer itself (Scheme 11.6).

In 1988, Hosomi et al. established that hydride transfer from hydrosilanes can be rendered enantioselective by using chiral anionic activators such as the dilithium salts of the diol **15** or of phenylalaninol **16** (Scheme 11.6) [22]. In the presence of stoichiometric amounts of the dilithium salt of **15**, isobutyrophenone was reduced by trialkoxysilanes with 69% ee, whereas 40 mol% of the corresponding salt of **16** was sufficient to effect reduction of acetophenone with 49% ee [23].

Kagan and Schiffers carefully studied the effect of the lithium salts of BINOL (**17**) and related axially chiral binaphthols on the reduction of a variety of ketones with trialkoxysilanes [24]. They found that diethyl ether, with TMEDA as an additive, was the best solvent for asymmetric reduction of ketones. In the presence of 5 mol% of the monolithium salt of BINOL (**17**), acetophenone (**1**) could be reduced with trimethoxysilane in 80% yield and with 61% ee. Enantiomeric excesses > 90% were achieved under the same conditions with 2′,4′,6′-trimethylacetophenone (**18**) or α-tetralone (**19**) as substrates. Aliphatic ketones such as



Scheme 11.6

4-phenyl-2-butanone (**20**) gave lower ee (46%), and racemic mixtures were obtained from benzophenones **21a**,**b** (Scheme 11.6) [24].

It should finally be mentioned that asymmetric reduction of prochiral ketones in chiral reverse micelles has also been attempted. Zhang et al. employed surfactants derived from ephedrine and achieved enantiomeric excesses up to 27% [25].

Conclusions

At the current stage of development of transition metal-free catalytic reductions the Corey–Bakshi–Shibata (CBS) method is the most widely applied procedure and affords excellent results for a wide range of ketone substrates. Substrates that can bind to metal ions and can thus inhibit transition metal catalysts are well tolerated by the CBS method, a typical advantage of transition metal-free catalytic methods. Borane reductions catalyzed by phosphoric amides also seem to have great potential. Recent years have seen remarkable improvement of the latter catalysts, and enantiomeric excesses ≥ 95% have been achieved. Both oxazaborolidine and phosphoric amide catalysts are of similar ready availability, but activity and selectivity are still higher for the former. An attractive feature of organocatalytic carbonyl reductions with silanes and, in particular, boranates is their even greater experimental simplicity. Significant potential for improvement can thus be seen in the further development of chiral activators or chiral phase-transfer catalysts for these purposes.

References

1 S. Itsuno, in: E. N. Jacobsen, A. Pfaltz, H. Yamamoto (Eds.) *Comprehensive Asymmetric Catalysis*, Springer, Berlin, 1999, pp. 289–315.

2 (a) E. J. Corey, C. J. Helal, *Angew. Chem.* **1998**, *110*, 2092–2118; *Angew. Chem. Int. Ed.* **1998**, *37*, 1986–2012; (b) L. Deloux, M. Srebnik, *Chem. Rev.* **1993**, *93*, 763–784; (c) S. Wallbaum, J. Martens, *Tetrahedron: Asymmetry* **1992**, *3*, 1475–1504.

3 E. J. Corey, R. K. Bakshi, S. Shibata, *J. Am. Chem. Soc.* **1987**, *109*, 5551–5553.

4 E. J. Corey, R. K. Bakshi, S. Shibata, C.-P. Chen, V. K. Singh, *J. Am. Chem. Soc.* **1987**, *109*, 7925–7926.

5 E. J. Corey, S. Shibata, R. K. Bakshi, *J. Org. Chem.* **1988**, *53*, 2861–2863.

6 S. Itsuno, A. Hirao, S. Nakahama, N. Yamazaki, *J. Chem. Soc., Perkin Trans. 1* **1983**, 1673–1676.

7 S. Itsuno, K. Ito, A. Hirao, S. Nakahama, *J. Chem. Soc., Chem. Commun.* **1983**, 469–470.

8 S. Itsuno, M. Nakano, K. Miyazaki, H. Masuda, K. Ito, A. Hirao, S. Nakahama, *J. Chem. Soc., Perkin Trans. 1* **1985**, 2039–2044.

9 H. Steinhagen, G. Helmchen, *Angew. Chem.* **1996**, *108*, 2489–2492; *Angew. Chem. Int. Ed.* **1996**, *35*, 2339–2342.

10 J. M. Brunel, G. Buono, *Topics Curr. Chem.* **2002**, *220*, 79–105.

11 G. Buono, O. Chiodi, M. Wills, *Synlett* **1999**, 377–388.

12 (a) B. Burns, J. R. Studley, M. Wills, *Tetrahedron Lett.* **1993**, *34*, 7105–7106; (b) B. Burns, N. P. King, J. R. Studley, H. Tye, M. Wills, *Tetrahedron: Asymmetry* **1994**, *5*, 801–804.

13 (a) J.-M. Brunel, O. Chiodi, B. Faure, F. Fotiadu, G. Buono, *J. Organomet. Chem.* **1997**, *529*, 285–294; (b) J.-M. Brunel, O. Pardigon, B. Faure, G. Buono, *J. Chem. Soc., Chem. Commun.* **1992**, 287–288.

14 V. Peper, J. Martens, *Tetrahedron Lett.* **1996**, *37*, 8351–8354.

15 O. Chiodi, F. Fotiadu, M. Sylvestre, G. Buono, *Tetrahedron Lett.* **1996**, *37*, 39–42.

16 (a) M. P. Gamble, J. R. Studley, M. Wills, *Tetrahedron Lett.* **1996**, *37*, 2853–2856; (b) M. P. Gamble, A. R. C. Smith, M. Wills, *J. Org. Chem.* **1998**, *63*, 6068–6071; (c) B. Burns,

N. P. King, H. Tye, J. R. Studley, M. Gamble, M. Wills, *J. Chem. Soc., Perkin Trans. 1* **1998**, 1027–1038; (d) M. P. Gamble, J. R. Studley, M. Wills, *Tetrahedron: Asymmetry* **1996**, *7*, 3071–3074.

17 J. M. Brunel, O. Legrand, G. Buono, *Eur. J. Org. Chem.* **2000**, 3313–3321.

18 M. F. P. Ma, K. Li, Z. Zhou, C. Tang, A. S. C. Chan, *Tetrahedron: Asymmetry* **1999**, *10*, 3259–3261.

19 P. Müller, P. Nury, G. Bernardinelli, *Helv. Chim. Acta* **2000**, *83*, 843–854.

20 S. Colonna, R. Fornasier, *J. Chem. Soc., Perkin Trans. 1* **1978**, 371–373.

21 M. D. Drew, N. J. Lawrence, W. Watson, S. A. Bowles, *Tetrahedron Lett.* **1997**, *38*, 5857–5860.

22 S. Kohra, H. Hayashida, Y. Tominaga, A. Hosomi, *Tetrahedron Lett.* **1988**, *29*, 89–92.

23 M. Hojo, A. Fuji, C. Murakami, M. Aihara, A. Hosomi, *Tetrahedron Lett.* **1995**, *36*, 571–574.

24 R. Schiffers, H. B. Kagan, *Synlett* **1997**, 1175–1178.

25 Y. Zhang, P. Sun, *Tetrahedron: Asymmetry* **1996**, *7*, 3055–3058.

12
Kinetic Resolution of Racemic Alcohols and Amines

12.1
Acylation Reactions

This chapter covers the kinetic resolution of racemic alcohols by formation of esters and the kinetic resolution of racemic amines by formation of amides [1]. The desymmetrization of meso diols is discussed in Section 13.3. The acyl donors employed are usually either acid chlorides or acid anhydrides. In principle, acylation reactions of this type are equally suitable for resolving or desymmetrizing the acyl donor (e.g. a *meso*-anhydride or a prochiral ketene). Transformations of the latter type are discussed in Section 13.1, Desymmetrization and Kinetic Resolution of Cyclic Anhydrides, and Section 13.2, Additions to Prochiral Ketenes.

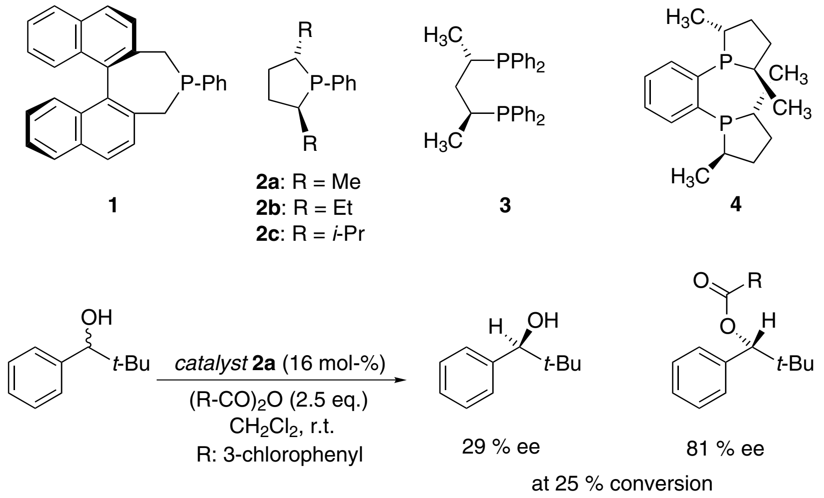
The organic acylation catalysts currently known are tertiary amines, *N*-heteroaromatic compounds (for example pyridine derivatives), or phosphines; they can be of central, planar, and axial chirality. Finally, small peptides carrying *N*-methylhistidine as the catalytically active subunit have also been employed; they also will be discussed in this chapter.

The kinetic resolution of racemic alcohols is probably the most intensively studied aspect of organocatalysis, and its beginnings can be traced back to the 1930s [2, 3]. In these early attempts naturally occurring alkaloids such as (−)-brucine and (+)-quinidine were used as catalysts. Synthetic chiral tertiary amines also were introduced and examined, and enantiomeric excesses up to ca. 45% were achieved up to the early 1990s [4, 5].

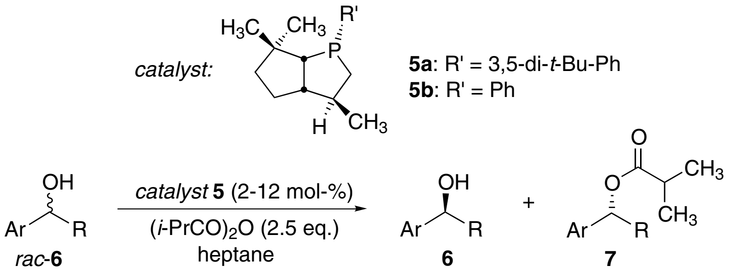
Significantly higher selectivity was reported for the first time in 1996 by Vedejs et al. using either the C_2-symmetric phosphines **1–4** [6, 8] (Scheme 12.1) or the bicyclic systems **5** (Scheme 12.2) [7, 8]. For example, selectivity factors in the range 12–15 were observed when phosphine **2a** was used in the acylation of aryl alkyl carbinols with 3-chlorobenzoic anhydride (Scheme 12.1).

The chiral bicyclic phosphines **5** (and in particular **5a** [7b]) are currently the most active phosphorus-based acylation catalysts, enabling use of low reaction temperatures. Under these conditions (i.e. −40 °C) selectivity factors as high as 370–390 were achieved (Scheme 12.2). This is the best selectivity factor *ever* reported for metal-free, non-enzymatic kinetic resolution. As a consequence, very good enantiomeric purity of both the isobutyric esters **7** and the remaining alcohols **6** was obtained, even at substrate conversions approaching 50% (Scheme 12.2) [7, 8].

Asymmetric Organocatalysis. Albrecht Berkessel and Harald Gröger
Copyright © 2005 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim
ISBN: 3-527-30517-3



Scheme 12.1



6,**7** Ar	**6**,**7** R	T [°C]	Catalyst (mol-%)	Conversion [%]	% ee **6**	% ee **7**	s
Ph	Me	rt	**5a** (4)	42	62	84	22
Ph	Me	-20	**5a** (2.5)	29	38	93	42
Ph	*n*-Bu	rt	**5a** (4)	39	54	83	18
Ph	*n*-Bu	-40	**5a** (4)	51	93	87	57
Ph	*t*-Bu	rt	**5b** (4)	53	89	79	24
Ph	*t*-Bu	-40	**5b** (5)	46	79	93	67
2-Tolyl	Me	rt	**5a** (3)	44	72	90	39
2-Tolyl	Me	-40	**5a** (4)	50	95	95	145
Mesityl	Me	rt	**5a** (4)	40	53	79	15
Mesityl	Me	-40	**5a** (12)	44	79	99	370-390
1-Naphthyl	Me	rt	**5a** (3)	42	66	90	41
1-Naphthyl	Me	-40	**5a** (4)	30	41	97	99

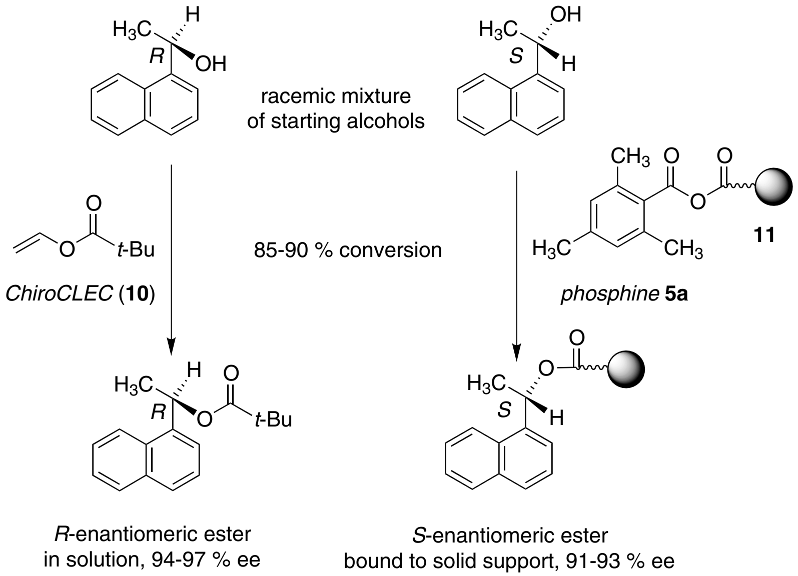
Scheme 12.2

Later, the chiral bicyclic phosphine catalyst **5a** was also used for kinetic resolution of allylic alcohols with isobutyric anhydride [8, 9]. The best results were obtained for trisubstituted allylic alcohols – selectivity factors ranged from 32 to 82 at −40 °C.

The Vedejs group also reported the centrally chiral DMAP derivatives **8** and **9** [10, 11].

8 **9**

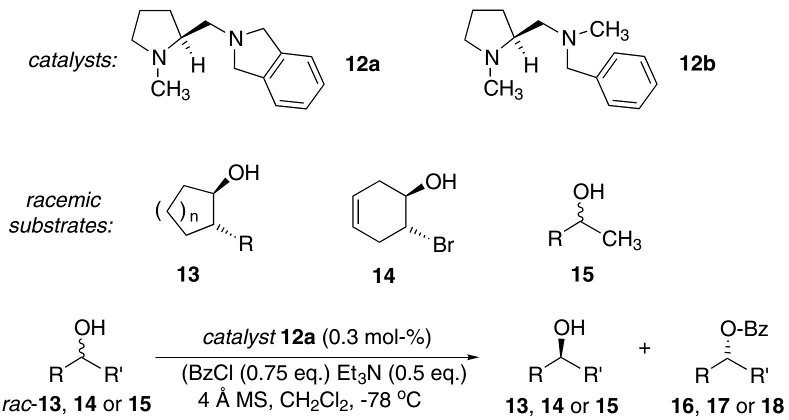
These chiral acyl donors can be used for quite effective kinetic resolution of racemic secondary alcohols. For example, enantiomeric aryl alkyl ketones are esterified by the acyl pyridinium ion **8** with selectivity factors in the range 12–53 [10]. In combination with its pseudo-enantiomer **9**, parallel kinetic resolution was performed [11]. Under these conditions, methyl 1-(1-naphthyl)ethanol was resolved with an "effective" selectivity factor > 125 [12]. Unfortunately, the acyl donors **8** and **9** must be preformed, and no simple catalytic version was reported. Furthermore, over-stoichiometric quantities of either $MgBr_2$ or $ZnCl_2$ are required to promote acyl transfer. In 2001, Vedejs and Rozners reported a *catalytic* parallel kinetic resolution of secondary alcohols (Scheme 12.3) [13].



Scheme 12.3

This quite remarkable process is based on simultaneous use of an insoluble lipase (ChiroCLEC, **10**, Scheme 12.3) and vinyl pivaloate for conversion of one enantiomer (*R*) of the substrate alcohol and of the solid-phase-bound anhydride **11** in combination with the phosphine **5a** for the conversion of the other enantiomer (*S*). This system meets the requirement that the soluble acyl donor (vinyl pivaloate) does not cross-react with the soluble catalyst (phosphine **5a**). After completion of the reaction the solid-phase-bound (*S*) enantiomer can easily be separated from the (*R*) product which remains in solution. As summarized in Scheme 12.3, this three-phase system affords remarkable yields and enantiomeric purity of the acylated alcohols [13].

Other centrally chiral amine catalysts reported for kinetic resolution of alcohols include the (*S*)-prolinol-derived dihydroisoindolines **12a**,**b** (Scheme 12.4), devel-



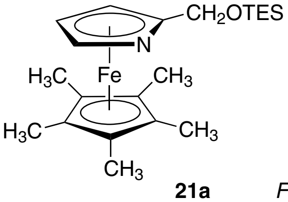
Substrate	Yield (ee) of **13**, **14** or **15** [%]	Yield (ee) of **16**, **17** or **18** [%]	s
rac-**13a** (n = 2; R = Ph)	49 (96) (1*S*, 2*R*)	48 (95) (1*R*, 2*S*)	160
rac-**13b** (n = 1; R = Ph)	45 (89) (1*S*, 2*R*)	42 (88) (1*R*, 2*S*)	37
rac-**13c** (n = 4; R = Ph)	44 (95)	47 (79)	88
rac-**13d** (n = 2; R = CO_2Et)	46 (85)	46 (90)	27
rac-**13e** (n = 2; R = CO_2*i*-Pr)	48(84)	46 (90)	27
rac-**13f** (n = 2; R = Br)	47 (96) (1*S*, 2*S*)	39 (95) (1*R*, 2*R*)	130
rac-**14**	46 (97) (1*S*, 2*S*)	43 (91) (1*R*, 2*R*)	170
rac-**15a** (R = Ph)	43 (69) (*S*)	41 (67) (*R*)	9
rac-**15b** (R = 2-tolyl)	45 (82)	49 (78)	20
rac-**15c** (R = Bn)	49 (46) (*S*)	39 (51) (*R*)	4

Scheme 12.4

oped by Oriyama [14], the chiral DMAP analog **19a** of Fuji and Kawabata [15], and the α-methylproline derivative **19b** of Campbell et al. (Scheme 12.5) [16]. The Oriyama catalyst **12a** is quite remarkable in that it can be applied at very low loadings (0.3 mol%) and still affords excellent selectivity (selectivity factors up to 170, Scheme 12.4). The related catalyst **12b** was also shown to differentiate between enantiomeric alcohols quite effectively (e.g. *rac*-**13a**, 5 mol% catalyst **12b**, selectivity factor 200). Because **12a** is significantly more reactive, however, in practice catalyst loadings can be kept lower than for **12b**.

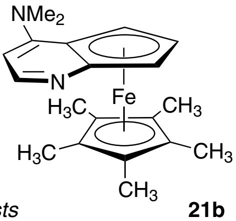
The DMAP derivative **19a** was tested for kinetic resolution of a variety of mono esters of cyclic cis diols (*rac*-**20a–i**) (Scheme 12.5) [15]. Catalyst **19a** afforded selectivity factors up to 12.3 and highly enantioenriched mono esters **20** with conversions of 65–73%. For this type of reaction the selectivity of the Campbell catalyst **19b** was similar (selectivity factor 13.2, Scheme 12.5) [16a]. The latter catalyst was identified by screening of a 31-mer library prepared from the parent *N*-(4-pyridyl)-α-methylproline and a variety of amines [16a]. The solid-phase-bound forms of *N*-(4-pyridyl)-α-methylproline, as reported by Anson et al. [16b], are easily recyclable acylation catalysts affording selectivity factors up to 11.9 in the kinetic resolution of the secondary alcohol *rac*-**20b** (Scheme 12.5). In the kinetic resolution of *N*-acylated amino alcohols, selectivity factors up to 21 were achieved by use of the Kawabata–Fuji catalyst **19a**, and up to 18.8 by use of the Campbell system **19b** (Scheme 12.5) [15, 16a].

Quite efficient nucleophilic catalysts with planar (**21a–c**) and axial (**22a–d**) chirality were recently developed by Fu et al. [17–22] and Spivey et al. [23–25]. The ferrocene-derived catalysts developed by Fu (**21a–c**) were first tested in the kinetic resolution of aryl alkyl carbinols with diketene as the acyl donor.

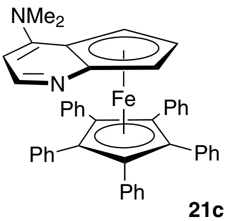


21a

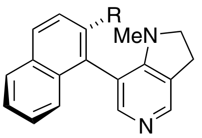
Fu's catalysts



21b

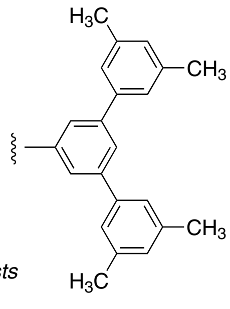


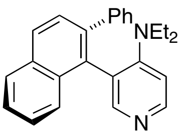
21c



22a: R = Me
22b: R = Ph

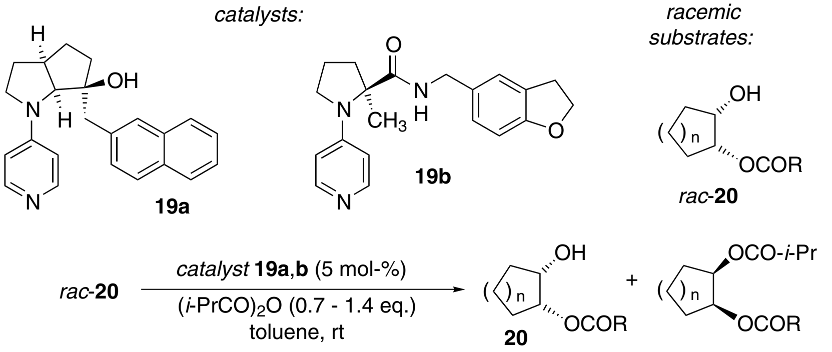
22c: R =





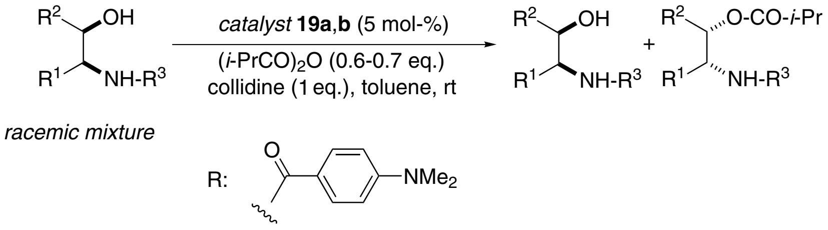
22d

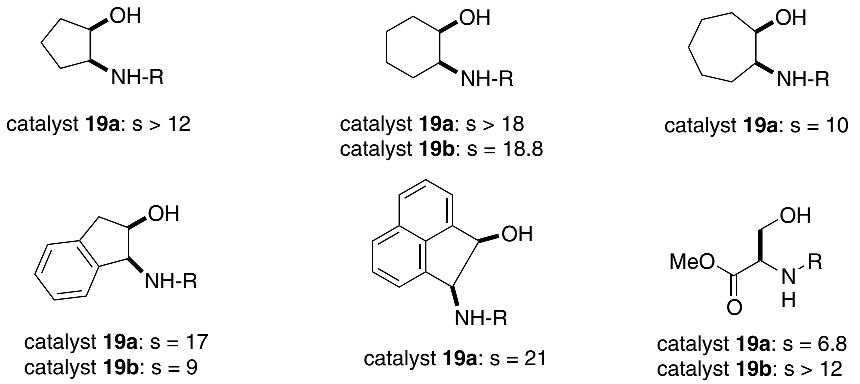
Spivey's catalysts



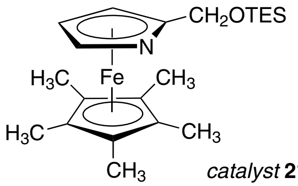
Substrate	Catalyst	Conversion of *rac*-**20** [%]	ee of remaining **20** [%]	s
rac-**20a** (n = 2; R = *t*-Bu)	**19a**	68	94	8.3
rac-**20b** (n = 2; R = 4-$Me_2NC_6H_4$)	**19a**	65	97	12.3
rac-**20b** (n = 2; R = 4-$Me_2NC_6H_4$)	**19b**	62	95	13.2
rac-**20c** (n = 1; R = 4-$Me_2NC_6H_4$)	**19a**	71	97	8.3
rac-**20d** (n = 3; R = 4-$Me_2NC_6H_4$)	**19a**	70	92	6.5
rac-**20e** (n = 4; R = 4-$Me_2NC_6H_4$)	**19a**	73	92	5.8

*Kinetic resolution of acylated amino alcohols using the catalysts **19a** and **19b**:*

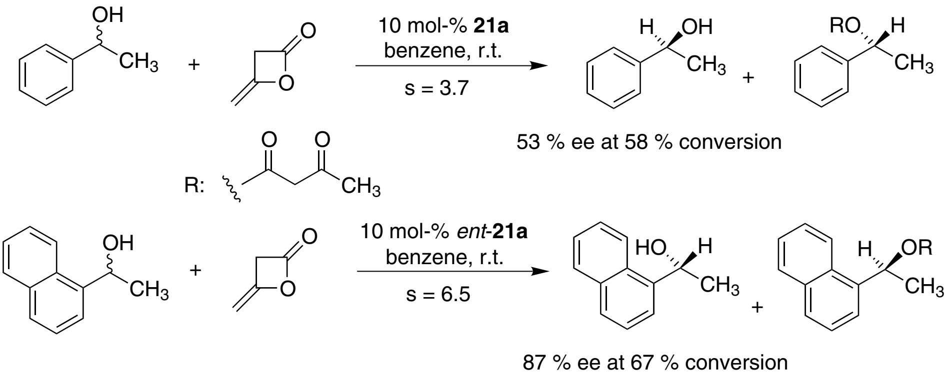




Scheme 12.5



catalyst **21a**



Scheme 12.6

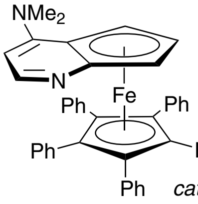
High reactivity was observed for **21b**, and **21a** was found to be the most selective. In the presence of 10 mol% **21a** selectivity factors as high as 6.5 were observed with racemic 1-(1-naphthyl)ethanol as substrate (Scheme 12.6) [18]. The TBS analog of **21a** was found to be good catalyst for asymmetric addition of methanol to a variety of prochiral aryl alkyl ketenes [18]. The catalytic asymmetric addition of achiral alcohols to prochiral ketenes is discussed in Section 13.2.

Later studies focused on the planar chiral DMAP derivative **21c** as catalyst and use of acetic anhydride as an inexpensive and readily available acyl donor [19]. Under these conditions (2 mol% catalyst loading, r.t.) kinetic resolution of several racemic alcohols could be achieved with selectivity factors up to 52 (Scheme 12.7). As a consequence, enantiomerically highly enriched alcohols ($\geq$ 95% ee) could be obtained at conversions only slightly above 50%.

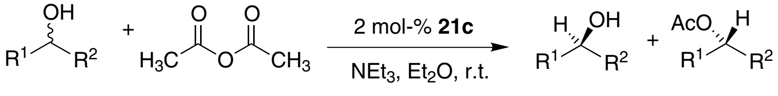
Significant further improvement of this process resulted from solvent screening. It was found that acylations proceed faster and with even higher selectivity in *tert*-amyl alcohol [20]. Scheme 12.8 illustrates the impressive performance of this easy-to-handle kinetic resolution which works almost perfectly even at catalyst loadings as low as 0.5 mol% [20].

As summarized in Schemes 12.9 and 12.10, kinetic resolution of propargylic [21] and allylic [22] alcohols work equally well. The DMAP–ferrocene hybrid **21c** was also used for kinetic resolution of racemic diols and for the desymmetrization of meso diols [20]. These two applications are discussed in Section 13.3.

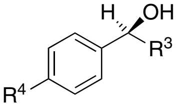
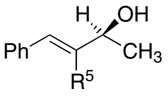
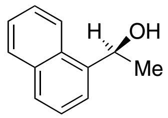
The axially chiral DMAP derivatives **22a–d** were developed by Spivey et al. [23–25]. In these catalysts the chiral axis is positioned meta to the pyridyl nitrogen



catalyst **21c**

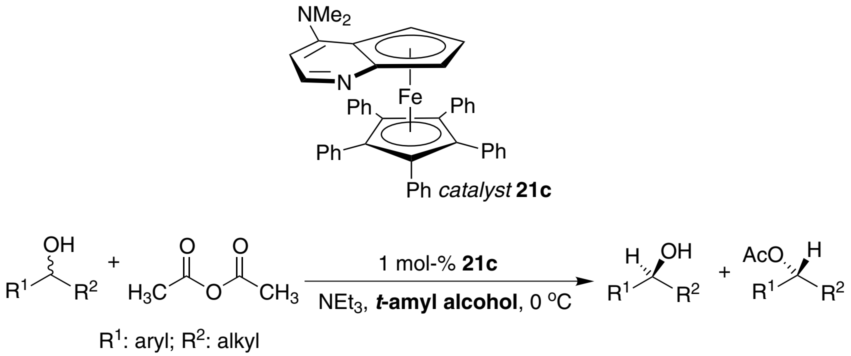


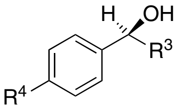
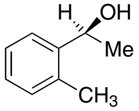
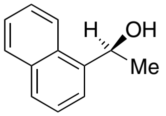
R^1: aryl, vinyl; R^2: alkyl

Remaining alcohol (major enantiomer)		Conversion of racemate [%]	ee of remaining alcohol [%]	s
	R^3 = Me; R^4 = H	62	95.2	14
	R^3 = Et; R^4 = H	62	98.8	20
	R^3 = *i*-Pr; R^4 = H	55	97.7	36
	R^3 = *t*-Bu; R^4 = H	51	92.2	52
	R^3 = CH_2Cl; R^4 = H	69	98.9	12
	R^3 = Me; R^4 = F	64	99.2	18
	R^3 = Me; R^4 = OMe	60	94.5	22
	R^5 = H	67	99.1	14
	R^5 = Me	61	99.0	22
		63	99.7	22

Scheme 12.7

atom. The rationale behind this type of structure is to maintain the high reactivity of unsubstituted DMAP and thus to enable use of low reaction temperatures and high selectivity. As shown in Scheme 12.11, selectivity factors less than ca. 5 were observed in initial experiments with the azaindolines **22a–c** [23, 24]. When the *N*,*N*-diethylpyridine catalyst **22d** (Scheme 12.11) was used, however, selectivity factors up to 29 were achieved. In the resolution of 1-(1-naphthyl)ethanol with isobu-



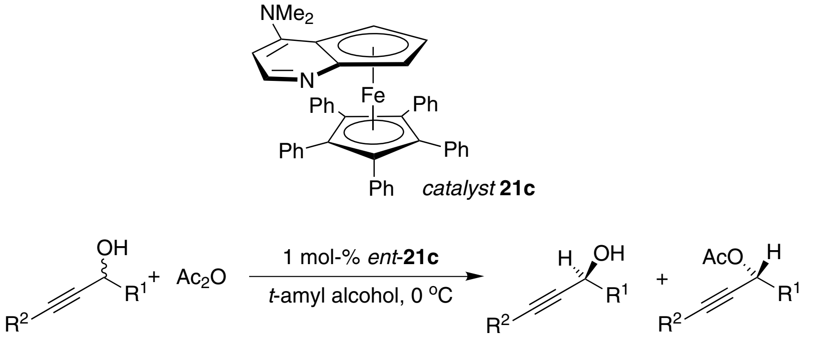
Remaining alcohol (major enantiomer)		Conversion of racemate [%]	ee of remaining alcohol [%]	s
	R^3 = Me; R^4 = H	55	99	43
	R^3 = *t*-Bu; R^4 = H	51	96	95
	R^3 = CH_2Cl; R^4 = H	56	98	32
	R^3 = Me; R^4 = F	54	99	68
		53	99	71
		52	95	65

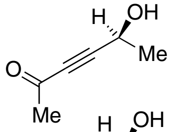
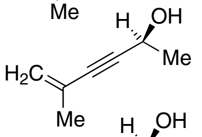
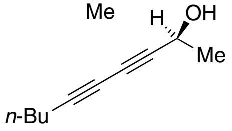
Scheme 12.8

tyric anhydride in toluene at −78 °C the (*R*)-ester could be obtained with an ee of 91% [25].

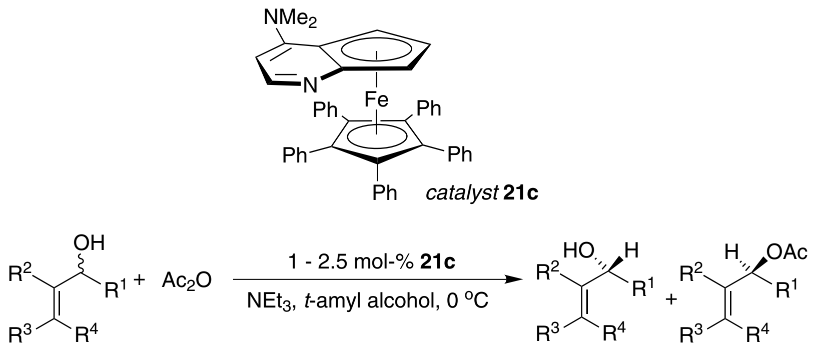
Jeong, Kim et al. reported use of the chiral DMAP derivative **22e**, which was synthesized from 3-amino-DMAP, Kemp's triacid, and *N*-acetyl-2,2′-diamino-1,1′-binaphthyl [26]. As summarized in Scheme 12.11, selectivity factors up to 21 were observed with 1 mol% modular catalyst **22e** in the kinetic resolution of a variety of secondary alcohols with acetic anhydride in *tert*-amyl alcohol as solvent, conditions first described by Fu et al. [20].

In addition to phosphines and pyridines, *N*-alkylated imidazoles are also known to act as a nucleophilic catalysts in acylation reactions [1]. In the approach by Miller et al. short oligopeptides incorporating *N*-alkylhistidine derivatives were used as enantioselective acylation catalysts [27]. The design of, e.g., the tripeptide



Substitution pattern	Conversion of racemate [%]	ee of remaining alcohol [%]	s
R^1 = Me; R^2 = Ph	58	96	20
R^1 = Et; R^2 = Ph	58	94	18
R^1 = *i*-Pr; R^2 = Ph	63	93	11
R^1 = *t*-Bu; R^2 = Ph	86	95	3.8
R^1 = Me; R^2 = 4-MeO-Ph	60	94	14
R^1 = Me; R^2 = 4-CF_3-Ph	71	99	10
R^1 = Me; R^2 = 4-F-Ph	65	97	13
	65	95	12
	69	94	7.9
	66	95	10

Scheme 12.9



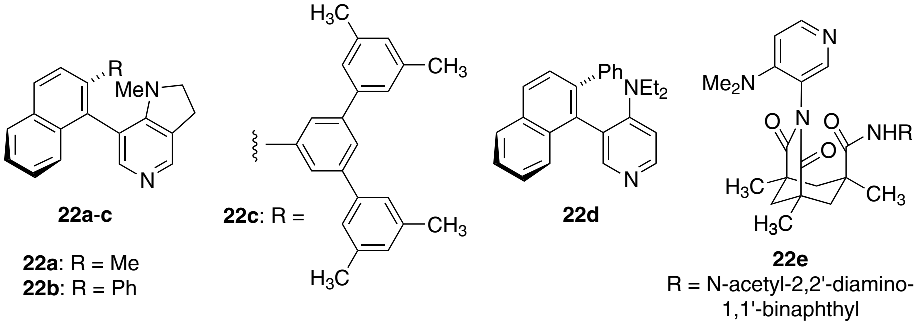
Substitution pattern	Conversion of racemate [%]	ee of remaining alcohol [%]	s
$R^1 = R^2 = Me$; $R^3 = Ph$; $R^4 = H$	53	98	80
$R^1 = Me$; $R^2 = H$; $R^3 = Ph$; $R^4 = H$	54	99	64
$R^1 = i$-Pr; $R^2 = R^3 = R^4 = Me$	59	99	29
$R^1 = i$-Pr; $R^2 = n$-Bu; $R^3 = R^4 = H$	55	94	25
$R^1 = i$-Pr; $R^2 = H$; $R^3 = R^4 = Me$	60	97	18
$R^1 = i$-Pr; $R^2 = Me$; $R^3 = R^4 = H$	58	93	17
$R^1 = i$-Pr; $R^2 = Ph$; $R^3 = R^4 = H$	59	93	14
$R^1 = n$-pentyl; $R^2 = H$; $R^3 = R^4 = Me$	66	97	12
$R^1 = Et$; $R^2 = Me$; $R^3 = R^4 = H$	63	93	11
$R^1 = R^2 = i$-Pr; $R^3 = R^4 = H$	63	92	10
$R^1 = i$-Pr; $R^2 = H$; $R^3 = n$-Pr; $R^4 = H$	75	92	5.4
$R^1 = i$-Pr; $R^2 = H$; $R^3 = H$; $R^4 = n$-Bu	73	90	5.3
$R^1 = n$-pentyl; $R^2 = i$-Pr; $R^3 = R^4 = H$	77	90	4.7

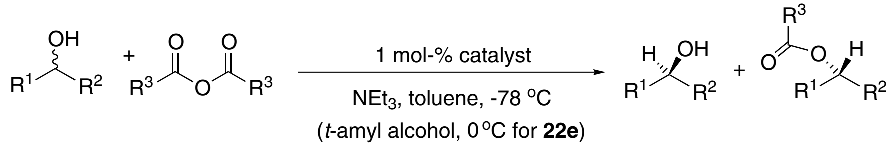
Scheme 12.10

23a [28] and the tetrapeptide **23b** [29] (Scheme 12.12) incorporates an *N*-alkylated and catalytically active His derivative, a Pro–Aib sequence to induce proper folding-back of the catalyst, and further elements of chirality (phenethylamine in **23a** and a fourth amino acid in **23b**).

The design of the peptide implies that interaction of the catalyst with its substrate relies heavily on hydrogen bonding. Initial studies indeed revealed that, in particular, *N*-acyl amino alcohols such as **25** and *ent*-**25** were efficiently differentiated whereas both enantiomers of 1-(1-naphthyl)ethanol were acetylated at identical rates [28]. Catalyst **23b**, shown in Scheme 12.12, was the most efficient from a series of ten peptides. For best performance, proper matching of the sense of chirality of all three chiral amino acids is necessary, and the type of amino acid present at the carbon terminus enables further tuning (for example, L-Phe was found to be better than, e.g., L-Val, selectivity factor 21) [29].

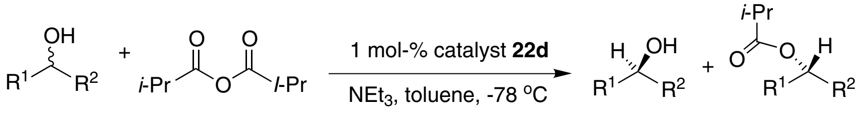
The Spivey-catalysts ***22a-d*** *and the Jeong-Kim-catalyst* ***22e****:*

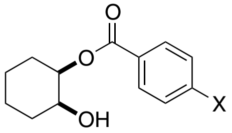
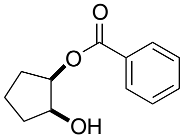
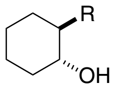
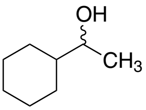




Substrate, acylating agent	Catalyst	Conversion of racemate [%]	ee of remaining alcohol [%]	ee of ester [%]	s
R^1 = Ph; R^2 = R^3 = Me	**22a**	35.0	9.1	19.6	1.5
R^1 = Ph; R^2 = R^3 = Me	**22b**	26.0	11.6	33.0	2.2
R^1 = Ph; R^2 = *i*-Pr; R^3 = Me	**22e**	77	99	31	8.1
R^1 = 1-naphthyl; R^2 = R^3 = Me	**22b**	18.3	9.0	40.1	2.5
R^1 = 1-naphthyl; R^2 = R^3 = Me	**22c**	17.6	13.1	61.2	4.7
R^1 = 1-naphthyl; R^2 = R^3 = Me	**22e**	72	98	38	8.3
R^1 = 1-naphthyl; R^2 = *t*-Bu; R^3 = Me	**22e**	63	95	57	12.4
R^1 = 1-naphthyl; R^2 = Me; R^3 = *i*-Pr	**22d**	17.2	18.6	89.3	21
R^1 = 1-naphthyl; R^2 = Me; R^3 = *i*-Pr	**22d**	22.3	26.3	91.4	29
R^1 = Ph; R^2 = Me; R^3 = *i*-Pr	**22d**	39.0	46.9	78.1	13
R^1 = *o*-tolyl; R^2 = Me; R^3 = *i*-Pr	**22d**	41.4	60.7	86.0	25
R^1 = Ph; R^2 = *t*-Bu; R^3 = *i*-Pr	**22d**	17.5	18.8	88.	20
R^1 = Ph; R^2 = *t*-Bu; R^3 = Me	**22e**	59	90	64	13.3
trans-2-phenylcyclohexanol; R^3 = Me	**22e**	62	99	62	21.0

Scheme 12.11



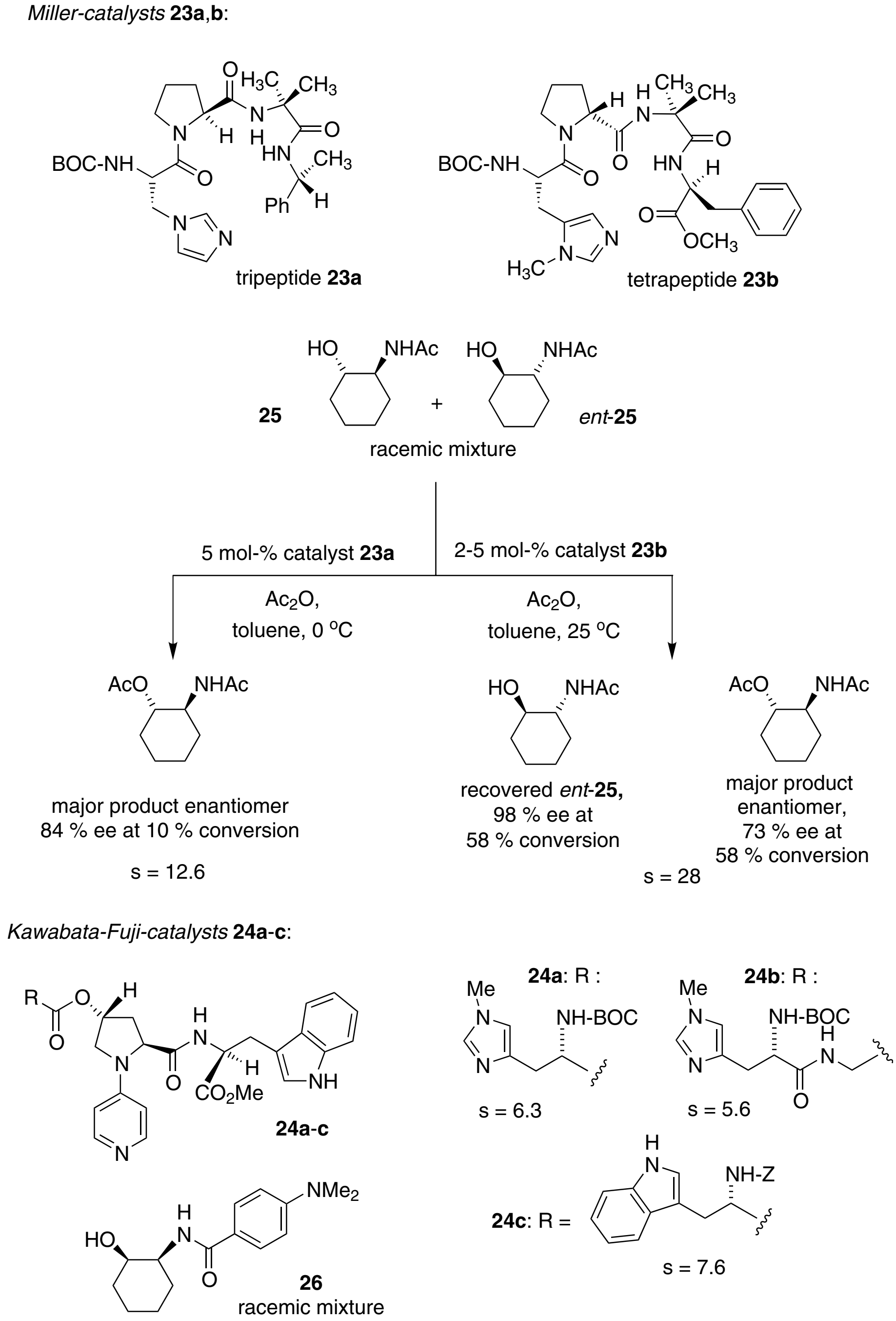
Racemic substrate		Conversion of racemate [%]	ee of remaining alcohol [%]	ee of ester [%]	s
	X = H	64.0	97.7	64.8	19.7
	X = NMe_2	18.0	17.9	86.4	16.1
	X = CN	11.0	8.2	67.2	5.5
	X = NO_2	69.0	85.3	39.1	5.7
		51.0	75.4	72.8	14.2
	R = Br	54.0	61.4	52.8	5.9
	R = Ph	16.0	14.3	78.0	9.3
		34.0	37.0	71.0	8.4

Scheme 12.11 (cont.)

Kawabata et al. found that peptides **24a–c** containing a 4-pyrrolidinopyridine (PPY) unit afford selectivity factors in the range 5.6–7.6 in the kinetic resolution of the *N*-acylated amino alcohol *rac*-**26** with *iso*-butyric anhydride (Scheme 12.12) [30]. In further studies by Miller et al. the octapeptide **27** was identified as even more enantioselective [31]. As shown in Scheme 12.13, selectivity factors as high as 51 were achieved.

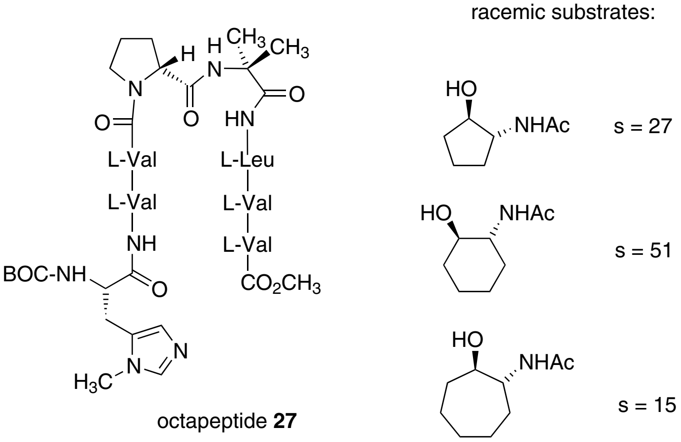
The modular structure of peptides and the well-established methods for their assembly enable the rapid synthesis of many structurally diverse catalyst candidates. For rapid screening of these Miller et al. developed the indicator **28** which becomes fluorescent on protonation (Scheme 12.14). In other words, catalyst candidates are usually incubated with acetic anhydride, the proton sensor **28** [32], and the two individual substrate enantiomers in *separate* microtiter plates. A related assay based on pH color indicators was developed by Davis et al. [34b].

Substrate acylation/liberation of acetic acid from the acylating agent results in fluorescence of **28**, and the relative rate of fluorescence increase is equal to



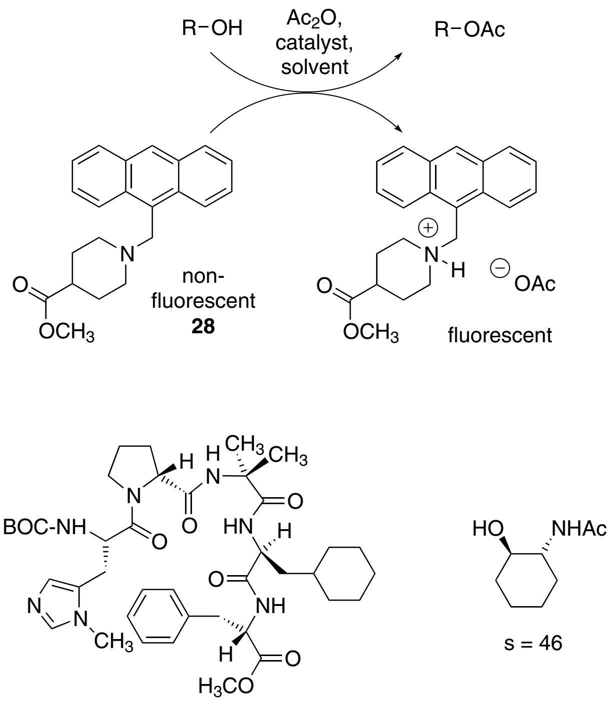
Miller-catalysts 23a,b:
tripeptide 23a
tetrapeptide 23b
25
ent-25
racemic mixture
5 mol-% catalyst 23a
2-5 mol-% catalyst 23b
Ac2O, toluene, 0 °C
Ac2O, toluene, 25 °C
major product enantiomer
84 % ee at 10 % conversion
s = 12.6
recovered ent-25,
98 % ee at
58 % conversion
major product enantiomer,
73 % ee at
58 % conversion
s = 28
Kawabata-Fuji-catalysts 24a-c:
24a-c
24a: R :
s = 6.3
24b: R :
s = 5.6
24c: R =
s = 7.6
26
racemic mixture

Scheme 12.12



octapeptide **27**

Scheme 12.13

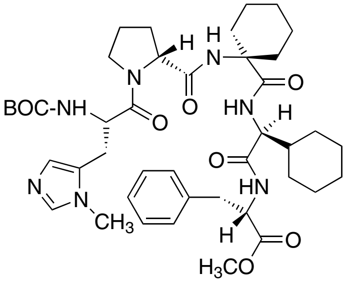


non-fluorescent **28**

pentapeptide **29**

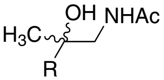
Scheme 12.14

the selectivity factor. By use of this method peptides **29** and **30** were identified from a 60-mer library comprising tetrapeptides and pentapeptides [35]. Whereas **29** distinguishes between the enantiomers of *trans*-2-acetaminocyclohexanol with a selectivity factor of 46 (Scheme 12.14), the pentapeptide **30** enables kinetic resolution of a series of tertiary alcohols with selectivity factors up to >50 (Scheme 12.15) [35].



pentapeptide **30**

racemic substrate alcohols



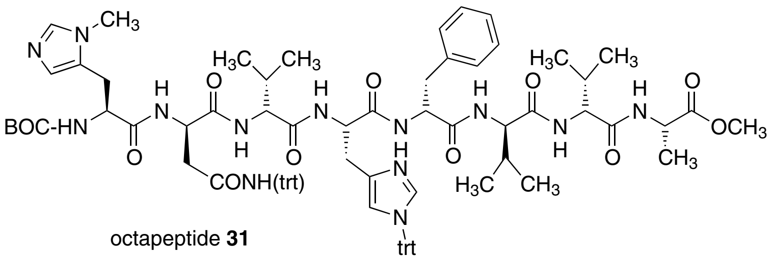
R	s (temp. [°C])
Ph	20 (4); 40 (-23)
4-Me-Ph	22 (4); > 50 (-23)
4-NO_2-Ph	15 (4); 32 (-23)
1-naphthyl	14 (4); 40 (-23)
5,6,7,8-tetrahydro-2-naphthyl	20 (4); 39 (-23)
cyclohexyl	9 (4); 19 (-23)

Scheme 12.15

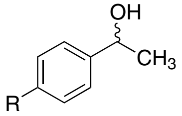
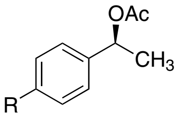
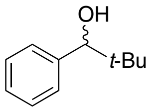
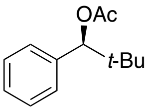
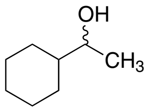
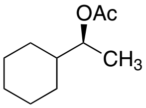
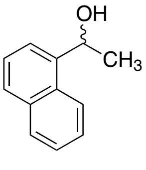
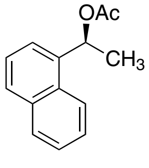
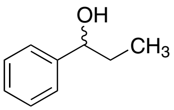
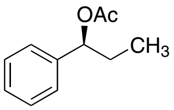
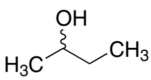
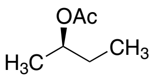
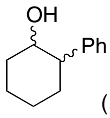
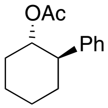
All the peptide catalysts discussed are selective for alcohol substrates that carry additional hydrogen bonding substituents (for example NHAc). In their search for catalysts that distinguish non-H-bonding substrates (for example 1-phenylethanol) Copeland and Miller screened a highly diverse 7.5×10^6-mer split-and-pool library of solid-phase-bound octapeptides, using the "sensor on the bead" method [33, 36]. Further optimization using a directed split-and-pool library afforded catalyst **31** which enables kinetic resolution of rather diverse "non-H-bonding" secondary alcohols with good to excellent (> 50) selectivity factors (Scheme 12.16).

By screening in solution Miller et al. identified the pentapeptide **32** as a catalyst for kinetic resolution of the alcohol *rac*-**33** (selectivity factor 27, Scheme 12.17). *rac*-**33** was an intermediate in their synthesis of enantiomerically pure mitosane **34** [37].

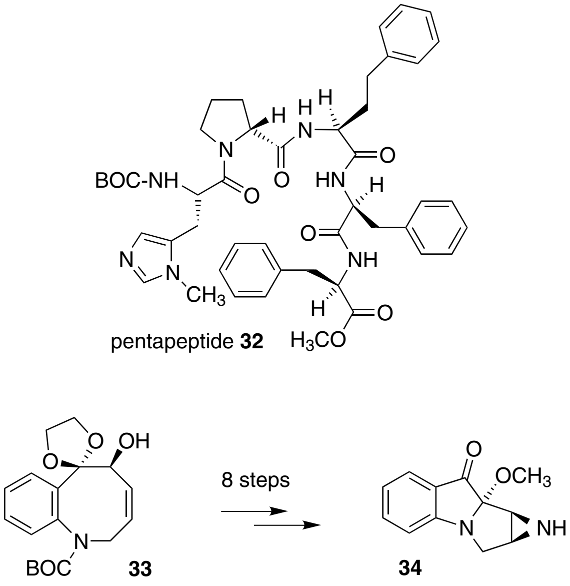
For all the substrates discussed so far the peptide catalysts employed had to differentiate between enantiomeric substrate molecules. Miller et al. subsequently screened peptide libraries for members able to selectively functionalize enantiotopic hydroxyl groups of meso inositols. In particular, they were able to convert *myo*-inositol **35** to *either* monophosphorylated D-*myo*-inositol-1-phosphate **37** *or* D-*myo*-inositol-3-phosphate *ent*-**37** in high yield and excellent ee (98%; Scheme 12.18) [38, 39]. This remarkable result was achieved by use of either of the penta-



octapeptide **31**

Racemic secondary substrate alcohols	Predominantly formed product enantiomer		s
		R = H R = OCH_3 R = F	20 16 11
			30
			9
			> 50
			8.2
			4.0
 (*trans*)			> 50

Scheme 12.16



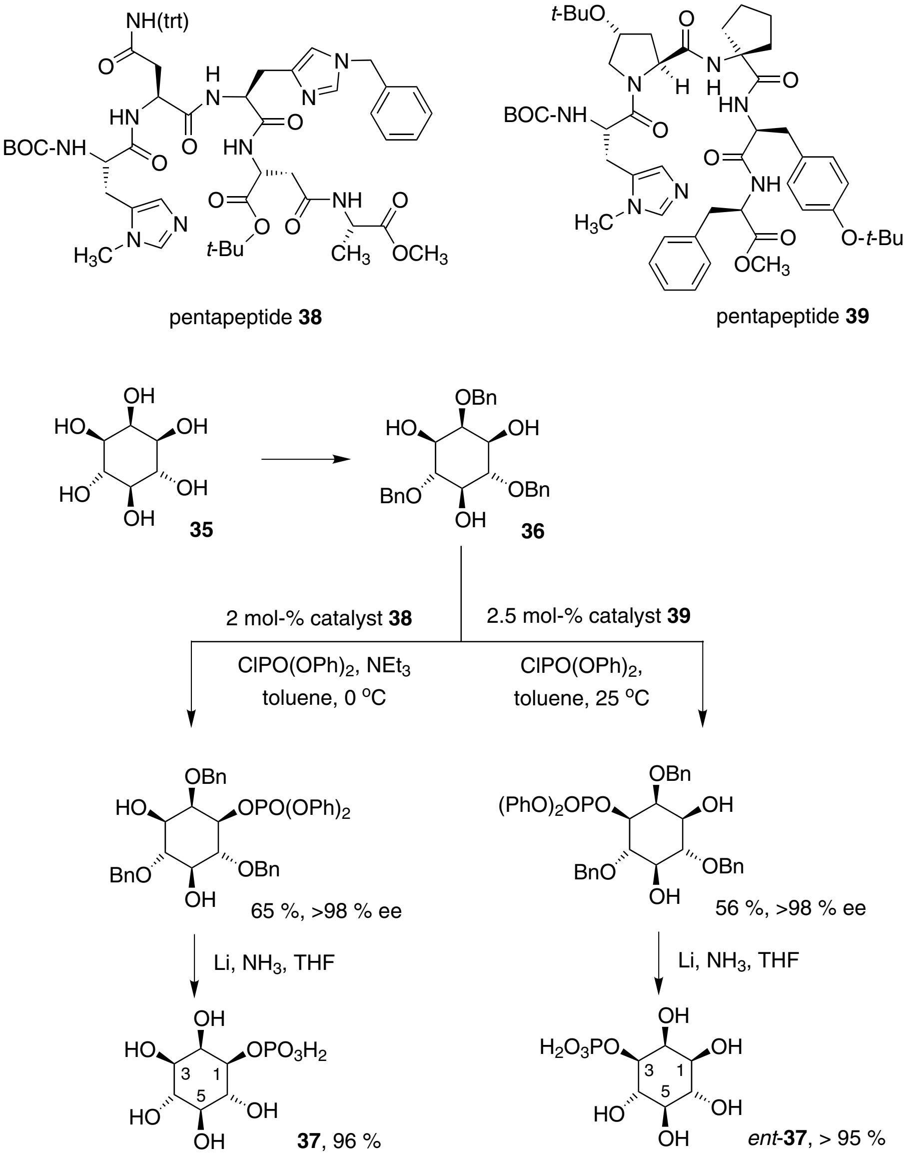
from *rac*-**33** using catalyst **32** (s = 27)
Scheme 12.17

peptides **38** or **39** as catalyst. In other words, peptides **38** and **39** are highly selective and complementary low-molecular-weight kinase mimics whereas the peptide catalysts already discussed have acylase activity. It is, furthermore, interesting to note that the opposite enantioselectivity of catalysts **38** and **39** could hardly have been predicted on the basis of the type and sequence of the amino acids involved.

Catalytic kinetic resolution of amines has been a typical domain of enzymatic transformations. Attempts to use low-molecular-weight catalysts have notoriously been frustrated by the rapid uncatalyzed background reaction of the amine substrate with the acyl donor [40]. The first solution to this problem was recently developed by Fu, who used the planar chiral catalyst **21d** and *O*-acyl azlactone **40** as the acyl donor (Scheme 12.19) [41]. In this process, the acyl transfer from the azlactone **40** to the nucleophilic catalyst **21d** is rapid relative to both direct transfer to the substrate and to the transfer from the acylated catalyst to the substrate amine. Under these conditions, which implies use of low reaction temperatures, selectivity factors as high as 27 were achieved (Scheme 12.19) [41].

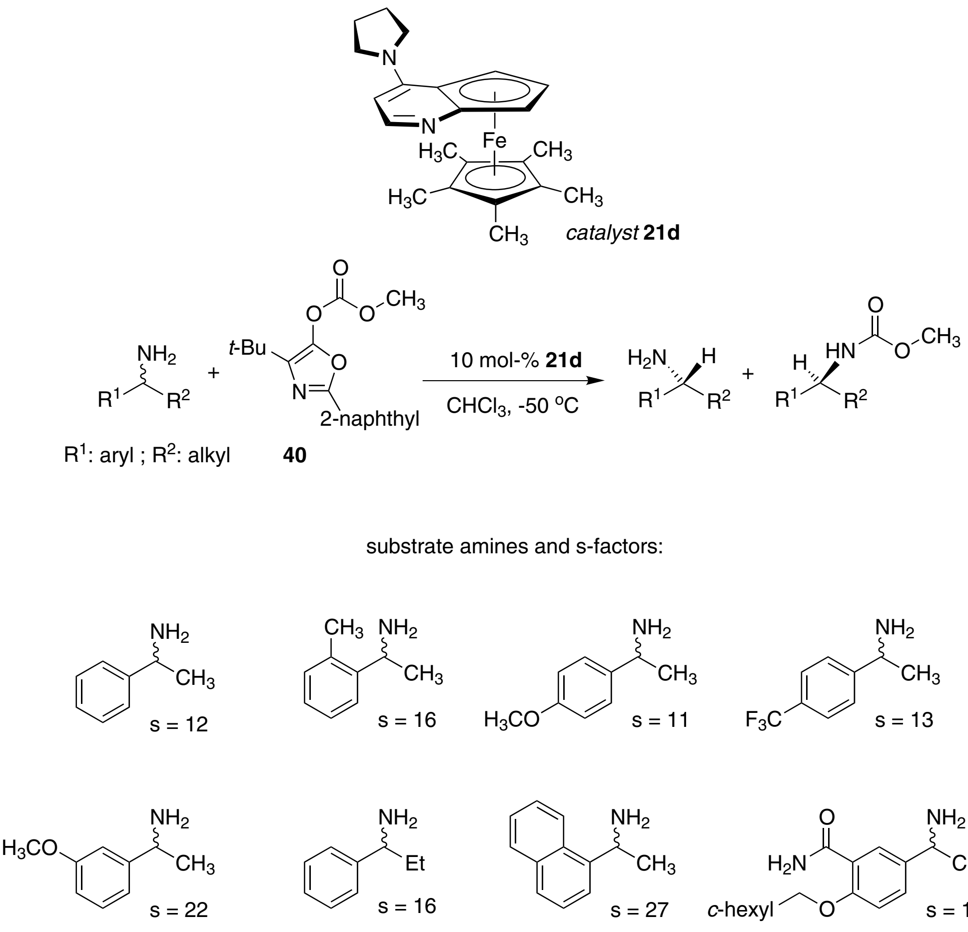
Conclusions

Recent years have seen enormous advances in the field of catalytic asymmetric acylations. Most of the work has been devoted to the kinetic resolution of racemic *alcohols*. For this application the most efficient catalysts currently available are



Scheme 12.18

the bicyclic phosphines introduced by Vedejs, the planar-chiral DMAP derivatives developed by Fu, and the peptide catalysts introduced by Miller. High selectivity has also been achieved with the chiral tertiary amine catalysts developed by Oriyama. All of these nucleophilic catalysts are well suited to practical applications. Practical selectivity is also achieved by use of the axially chiral DMAP derivatives of Spivey.

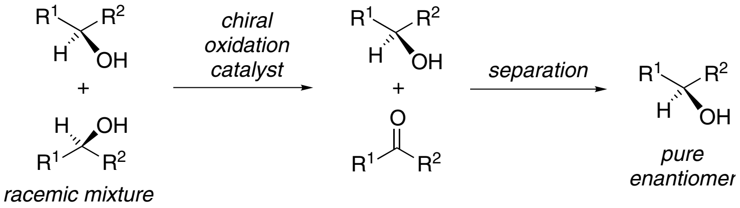


Scheme 12.19

It is especially worth noting that a method for non-enzymatic resolution of *amines* by acylation has also been developed. It is hoped that selectivity factors and ease of operation achieved in the kinetic resolution of alcohols will soon by possible with amines also.

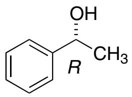
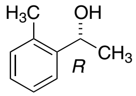
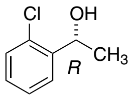
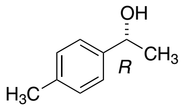
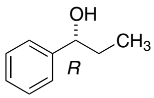
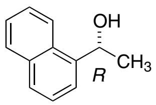
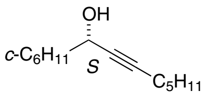
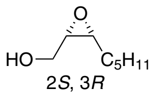
12.2 Redox Reactions

Kinetic resolution relies on enantiospecific conversion of one enantiomer present in a racemic mixture while the other remains unchanged (except for *parallel* kinetic resolution in which both enantiomers are transformed but to *different* products). For secondary alcohols enantiospecific conversion might consist in oxidation of one enantiomer to a ketone while the other remains unchanged (Scheme 12.20).

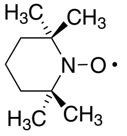


Scheme 12.20

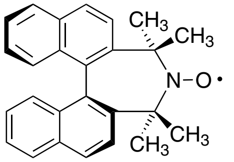
Tab. 12.1

mol-% 87	*Recovered alcohol*	*ee (%)*	*Conversion (%)*	*S*
0.5		81	69	5.0
1.0		98	87	7.1
1.0		73	58	6.8
1.0		89	70	6.0
1.0		64	58	5.1
1.0		57	59	3.9
0.5		57	56	4.5
0.5		41	66	2.2
0.5		19	58	1.5

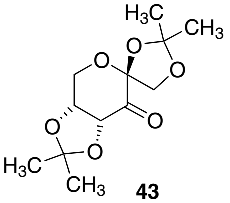
Oxidation of alcohols to carbonyl compounds using the stable nitroxyl radical TEMPO (**41**) as catalyst is a well-known preparative method [42, 43]. Hypochlorite or peracetic acid is usually used as the final oxidizing agent and ca. 1 mol% of the catalyst **41** is used. In 1996 Rychnovsky et al. reported the synthesis of the chiral, binaphthyl-derived TEMPO analog **42** [44]. Table 12.1 lists the results obtained with 0.5–1 mol% of catalyst **42** [44]. In these oxidation reactions 0.6–0.7 equivalents of sodium hypochlorite were used as the final oxidizing agent (plus 0.1 equiv. potassium bromide) in a two-phase system containing substrate and catalyst **42** in dichloromethane at 0 °C. As shown, the best selectivity factors (≥ 5) were observed for 1-phenylethanol and its derivatives as substrates.



41



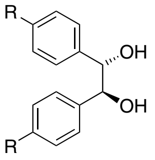
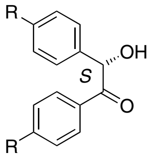
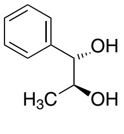
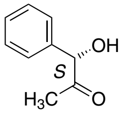
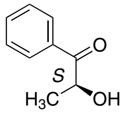
42



43

Whereas the chiral TEMPO analog **42** was used to resolve racemic secondary alcohols the D-fructose-derived ketone **43** [45] proved useful for oxidative resolution of racemic diols (Table 12.2) [46, 47]. Persulfate in the form of Oxone, Curox, etc., serves as the final oxidizing agent, and the dioxirane generated from the ketone **43** is the chiral active species. Because of the relatively low conversions (except for the unsubstituted dihydrobenzoin) at which the stated ee were achieved, the method currently seems to be of limited practical value. Three equivalents of ketone **43** were typically used [46, 47].

Tab. 12.2

Starting racemic diol	*Conversion (%)*		*Product hydroxy ketone*	*ee (%)*
	R = H	51		65
	R = CH_3	12		61
	R = F	31		69
	R = Cl	11		70
	R = Br	10		74
	R = CN	6		75
		20		44
				69

Conclusions

In principle, oxidative kinetic resolution of racemic alcohols can be achieved by using chiral oxidation catalysts such as TEMPO derivatives or dioxiranes. The selectivity achieved by use of these methods is, however, less than that observed in acylation reactions (Section 12.1).

References

1 (a) For a review of acyl-transfer catalysis by both Lewis acids and nucleophiles see: A. C. Spivey, A. Maddaford, *Org. Prep. Proc. Int.* **2000**, *32*, 331–365; (b) for a leading review on the preparation and catalytic properties of DMAP see: G. Höfle, W. Steglich, H. Vorbrüggen, *Angew. Chem.* **1978**, *90*, 602–615; *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 569–583; (c) for a recent review on nucleophilic chiral amine catalysts see: S. France, D. J. Guerin, S. J. Miller, T. Lectka, *Chem. Rev.* **2003**, *103*, 2985–3012; (d) for a recent review on polymer-supported organic catalysts see: M. Benaglia, A. Puglisi, F. Cozzi, *Chem. Rev.* **2003**, *103*, 3401–3429.

2 R. Wegler, *Liebigs Ann. Chem.* **1932**, *498*, 62; *ibid.* **1933**, *506*, 77–83; *ibid.* **1934**, *510*, 72–87.

3 R. Wegler, A. Ruber, *Chem. Ber.* **1935**, *68*, 1055–1059.

4 P. J. Weidert, E. Geyer, L. Horner, *Liebigs Ann. Chem.* **1989**, 533–538.

5 V. M. Popatov, V. M. Dem'yanovich, V. A. Khlebnikov, *J. Gen. Chem. USSR* **1988**, *24*, 301–305; *Zh. Org. Khim.* **1988**, *24*, 343–348.

6 (a) E. Vedejs, O. Daugulis, S. T. Diver, *J. Org. Chem.* **1996**, *61*, 430–431; (b) E. Vedejs, O. Daugulis, N. Tuttle, *J. Org. Chem.* **2004**, *69*, 1389–1392.

7 (a) E. Vedejs, O. Daugulis, *J. Am. Chem. Soc.* **1999**, *121*, 5813–5814; (b) E. Vedejs, O. Daugulis, *J. Am. Chem. Soc.* **2003**, *125*, 4166–4173; (c) E. Vedejs, O. Daugulis, L. A. Harper, J. A. MacKay, D. R. Powell, *J. Org. Chem.* **2003**, *68*, 5020–5027.

8 For an account of enantioselective acyl transfer reactions using chiral phosphine catalysts see: E. Vedejs, O. Daugulis, J. A. MacKay, E. Rozners, *Synlett* **2001**, 1499–1505.

9 E. Vedejs, J. A. MacKay, *Org. Lett.* **2001**, *3*, 535–536.

10 E. Vedejs, X. Chen, *J. Am. Chem. Soc.* **1996**, *118*, 1809–1810.

11 For a recent highlight on the parallel kinetic resolution of racemic mixtures, see: J. Eames, *Angew. Chem.* **2000**, *112*, 913–916; *Angew. Chem. Int. Ed.* **2000**, *39*, 885–888.

12 E. Vedejs, X. Chen, *J. Am. Chem. Soc.* **1997**, *119*, 2584–2585.

13 E. Vedejs, E. Rozners, *J. Am. Chem. Soc.* **2001**, *123*, 2428–2429.

14 T. Sano, K. Imai, K. Ohashi, T. Oriyama, *Chem. Lett.* **1999**, 265–266.

15 (a) T. Kawabata, M. Nagato, K. Takasu, K. Fuji, *J. Am. Chem. Soc.* **1997**, *119*, 3169–3170; (b) T. Kawabata, K. Yamamoto, Y. Momose, H. Yoshida, Y. Nagaoka, K. Fuji, *J. Chem. Soc., Chem. Commun.* **2001**, 2700–2701; (c) T. Kawabata, R. Stragies, T. Fukaya, Y. Nagaoka, H. Schedel, K. Fuji, *Tetrahedron Lett.* **2003**, *44*, 1545–1548.

16 (a) G. Priem, B. Pelotier, S. J. F. Macdonald, M. S. Anson, I. B. Campbell, *J. Org. Chem.* **2003**, *68*, 3844–3848; (b) B. Pelotier, G. Priem, I. B. Campbell, S. J. F. Macdonald, M. S. Anson, *Synlett* **2003**, 679–683.

17 Surveys: G. C. Fu, *Acc. Chem. Res.* **2000**, *33*, 412–420; *Pure Appl. Chem.* **2001**, *73*, 347–349; *Pure Appl. Chem.* **2001**, *73*, 1113–1116.

18 (a) J. C. Ruble, G. C. Fu, *J. Org. Chem.* **1996**, *61*, 7230–7231; (b) B. L. Hodous, J. C. Ruble, G. C. Fu, *J. Am. Chem. Soc.* **1999**, *121*, 2637–2638.

19 J. C. Ruble, H. A. Latham, G. C. Fu, *J. Am. Chem. Soc.* **1997**, *119*, 1492–1493.

20 J. C. Ruble, J. Twedell, G. C. Fu, *J. Org. Chem.* **1998**, *63*, 2794–2795.

21 B. Tao, J. C. Ruble, D. A. Hoic, G. C. Fu, *J. Am. Chem. Soc.* **1999**, *121*, 5091–5092.

22 S. Bellemin-Laponnaz, J. Twedell, J. C. Ruble, F. M. Breitling, G. C. Fu, *J. Chem. Soc., Chem. Commun.* **2000**, 1009–1010.

23 A. C. Spivey, T. Fekner, H. Adams, *Tetrahedron Lett.* **1998**, *39*, 8919–8922.

24 A. C. Spivey, T. Fekner, S. E. Spey, H. Adams, *J. Org. Chem.* **1999**, *64*, 9430–9443.

25 (a) A. C. Spivey, T. Fekner, S. E. Spey, *J. Org. Chem.* **2000**, *65*, 3154–3159; (b) A. C. Spivey, F. Zhu, M. B. Mitchell, S. G. Davey, R. L. Jarvest, *J. Org. Chem.* **2003**, *68*, 7379–7385.

26 K.-S. Jeong, S.-H. Kim, H.-J. Park, K.-J. Chang, K. S. Kim, *Chem. Lett.* **2002**, 1114–1115.

27 For a recent review on amino acids and peptides as asymmetric organocatalysts see: E. R. Jarvo, S. J. Miller, *Tetrahedron* **2002**, *58*, 2481–2495.

28 S. J. Miller, G. T. Copeland, N. Papaioannou, T. E. Horstmann, E. M. Ruel, *J. Am. Chem. Soc.* **1998**, *120*, 1629–1630.

29 (a) G. T. Copeland, E. R. Jarvo, S. J. Miller, *J. Org. Chem.* **1998**, *63*, 6784–6785; (b) For a conformational analysis of His–Pro–Aib peptides see: J. T. Blank, D. J. Guerin, S. J. Miller, *Org. Lett.* **2000**, *2*, 1247–1249.

30 T. Kawabata, R. Stragies, T. Fukaya, Y. Nagaoka, H. Schedel, K. Fuji, *Tetrahedron Lett.* **2003**, *44*, 1545–1548.

31 E. R. Jarvo, G. T. Copeland, N. Papaioannou, P. J. Bonitatebus, Jr., S. J. Miller, *J. Am. Chem. Soc.* **1999**, *121*, 11638–11643.

32 In combination with peptide catalysts for kinetic resolution of alcohols, aminomethyl anthracene derivatives such as **28** have been used in homogeneous solution and as bead-bound sensors [33] and in polymeric PEGA gels [34a].

33 G. T. Copeland, S. J. Miller, *J. Am. Chem. Soc.* **1999**, *121*, 4306–4307.

34 (a) R. F. Harris, A. J. Nation, G. T. Copeland, S. J. Miller, *J. Am. Chem. Soc.* **2000**, *122*, 11270–11271; (b) M. Müller, T. W. Mathers, A. P. Davis, *Angew. Chem.* **2001**, *113*, 3929–3931; *Angew. Chem. Int. Ed.* **2001**, *40*, 3813–3815.

35 E. R. Jarvo, C. A. Evans, G. T. Copeland, S. J. Miller, *J. Org. Chem.* **2001**, *66*, 5522–5527.

36 G. T. Copeland, S. J. Miller, *J. Am. Chem. Soc.* **2001**, *123*, 6496–6502.

37 N. Papaioannou, C. A. Evans, J. T. Blank, S. J. Miller, *Org. Lett.* **2001**, *3*, 2879–2882.

38 B. R. Sculimbrene, S. J. Miller, *J. Am. Chem. Soc.* **2001**, *123*, 10125–10126.

39 B. R. Sculimbrene, A. J. Morgan, S. J. Miller, *J. Am. Chem. Soc.* **2002**, *124*, 11653–11656.

40 For a stoichiometric kinetic resolution of amines, using preformed *N*-acyl derivatives of ferrocenyl DMAP derivatives see: Y. Ie, G. C. Fu, *J. Chem. Soc., Chem. Commun.* **2000**, 119–120.

41 S. Arai, S. Bellemin-Laponnaz, G. C. Fu, *Angew. Chem.* **2001**, *113*, 240–242; *Angew. Chem. Int. Ed.* **2001**, *40*, 234–236.

42 P. L. Anelli, F. Montanari, S. Quici, *Org. Synth.* **1990**, *69*, 212–219.

43 P. L. Anelli, S. Banfi, F. Montanari, S. Quici, *J. Org. Chem.* **1989**, *54*, 2970–2972.

44 (a) S. D. Rychnovsky, T. L. McLernon, H. Rajapakse, *J. Org. Chem.* **1996**, *61*, 1194–1195; (b) For a review on optically active nitroxides, see: N. Naik, R. Braslav, *Tetrahedron* **1998**, *54*, 667–696.

45 M. Frohn, Y. Shi, *Synthesis* **2000**, 1979–2000.

46 W. Adam, C. R. Saha-Möller, C.-G. Zhao, *Tetrahedron: Asymmetry* **1998**, *9*, 4117–4122.

47 W. Adam, C. R. Saha-Möller, C.-G. Zhao, *J. Org. Chem.* **1999**, *64*, 7492–7497.

13
Desymmetrization and Kinetic Resolution of Anhydrides; Desymmetrization of *meso*-Epoxides and other Prochiral Substrates

13.1
Desymmetrization and Kinetic Resolution of Cyclic Anhydrides

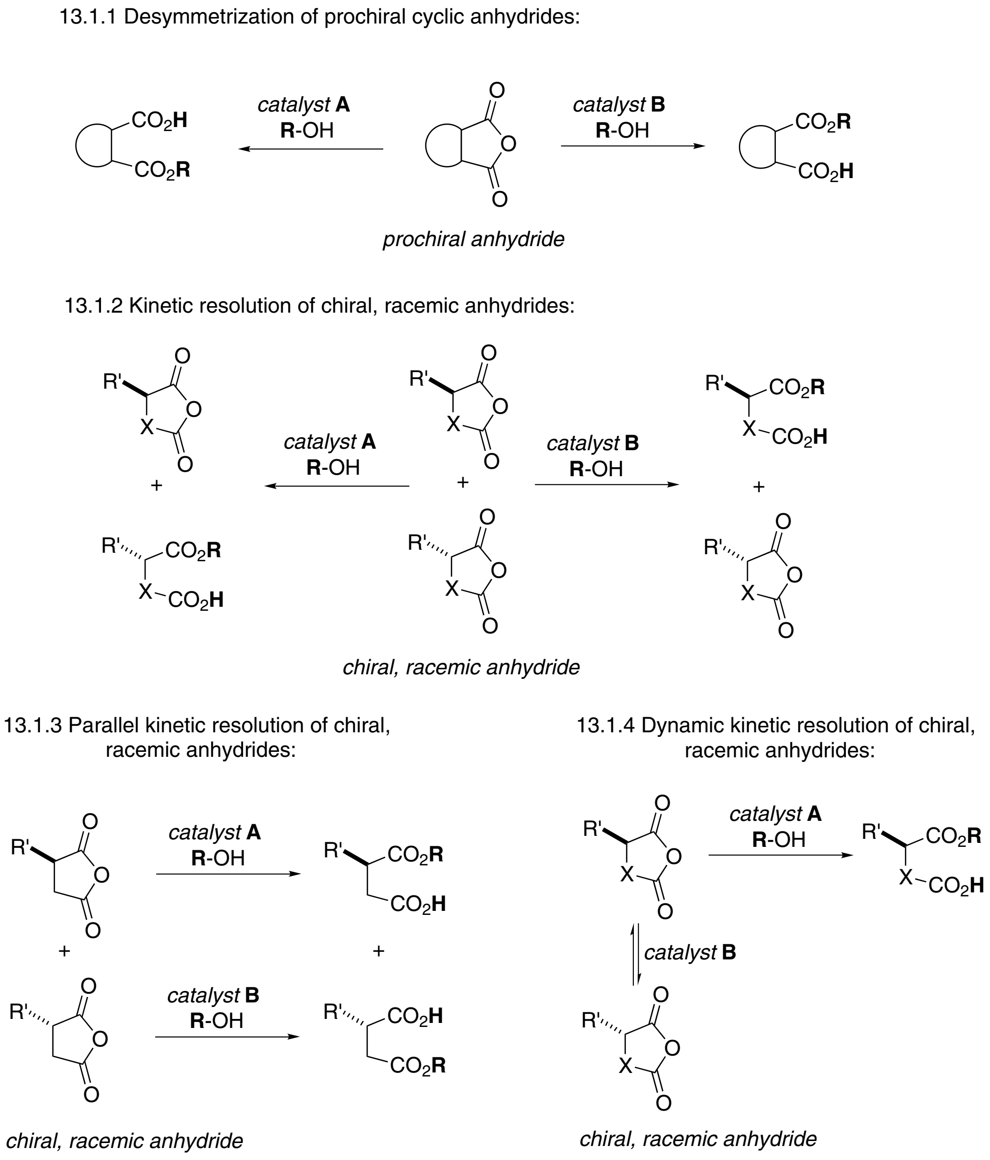
Most work on this subject is based on the use of *alcohols* as reagents in the presence of enantiomerically pure nucleophilic catalysts [1, 2]. This section is subdivided into four parts on the basis of classes of anhydride substrate and types of reaction performed (Scheme 13.1) – desymmetrization of prochiral cyclic anhydrides (Section 13.1.1); kinetic resolution of chiral, racemic anhydrides (Section 13.1.2); parallel kinetic resolution of chiral, racemic anhydrides (Section 13.1.3); and dynamic kinetic resolution of racemic anhydrides (Section 13.1.4).

Desymmetrization of prochiral cyclic anhydrides: In the presence of the chiral nucleophilic catalyst (e.g. **A**, Scheme 13.1, top) one of the enantiotopic carbonyl groups of the *prochiral* (usually *meso*) cyclic anhydride substrate is selectively converted into an ester. Application of catalyst **B** (usually the enantiomer or a pseudo-enantiomer of **A**) results in generation of the enantiomeric product ester. Ideally, 100% of one enantiomerically pure product can be generated from the starting anhydride. No reports of desymmetrizing alcoholyses of *acyclic* meso anhydrides appear to exist in the literature.

Kinetic resolution of chiral, racemic anhydrides: In this process the racemic mixture of a *chiral* anhydride is exposed to the alcohol nucleophile in the presence of a chiral catalyst such as **A** (Scheme 13.2, middle). Under these conditions, one substrate enantiomer is converted to a mono-ester whereas the other remains unchanged. Application of catalyst **B** (usually the enantiomer or a pseudo-enantiomer of **A**) results in transformation/non-transformation of the enantiomeric starting anhydride(s). As usual for kinetic resolution, substrate conversion/product yield(s) are intrinsically limited to a maximum of 50%. For "normal" anhydrides ($X = CR_2$), both carbonyl groups can engage in ester formation, and the product formulas in Scheme 13.1 are drawn arbitrarily. This section also covers the catalytic asymmetric alcoholysis of α-hydroxy acid *O*-carboxy anhydrides (X = O) and of α-amino acid *N*-carboxy anhydrides (X = NR). In these reactions the electrophilicity of the carbonyl groups flanking "X" is reduced and regioselective attack of the alcohol nucleophile on the other carbonyl function results.

Parallel kinetic resolution of chiral, racemic anhydrides: The term parallel kinetic resolution (PKR) implies that the two substrate enantiomers (Scheme 13.1, bottom

Asymmetric Organocatalysis. Albrecht Berkessel and Harald Gröger
Copyright © 2005 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim
ISBN: 3-527-30517-3



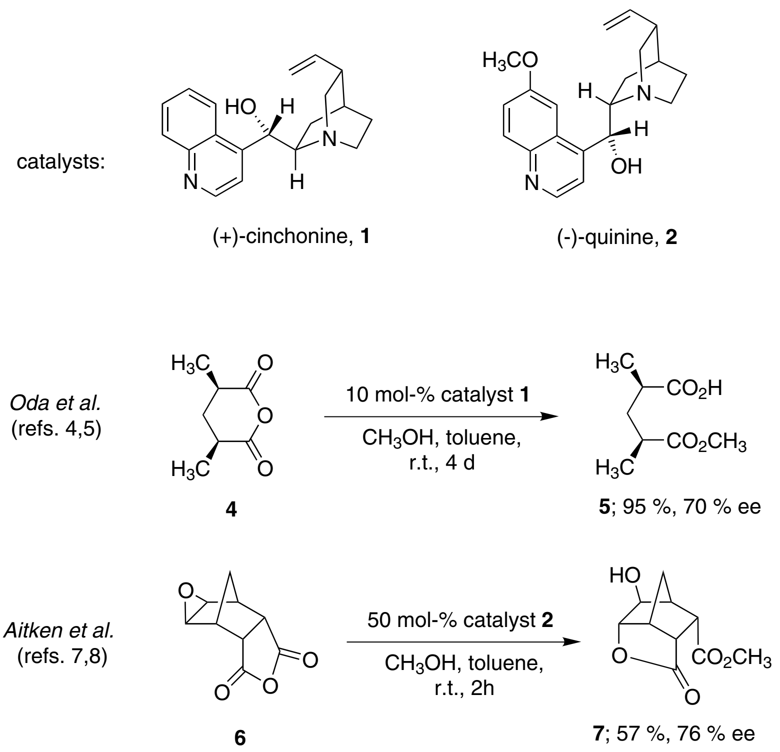
Scheme 13.1

left) are converted into different products in the course of the reaction, ideally at identical rates [3]. If there is just one reaction partner, i.e. the alcohol nucleophile R–OH, the regioselectivity of attack on the two carbonyl groups is the only means of generating chemically distinct products. The catalysts **A** and **B** can be enantiomers or pseudo-enantiomers. *One* chiral catalyst (**A** = **B**) might, however, effect the conversion of *both* anhydride enantiomers to the isomeric products.

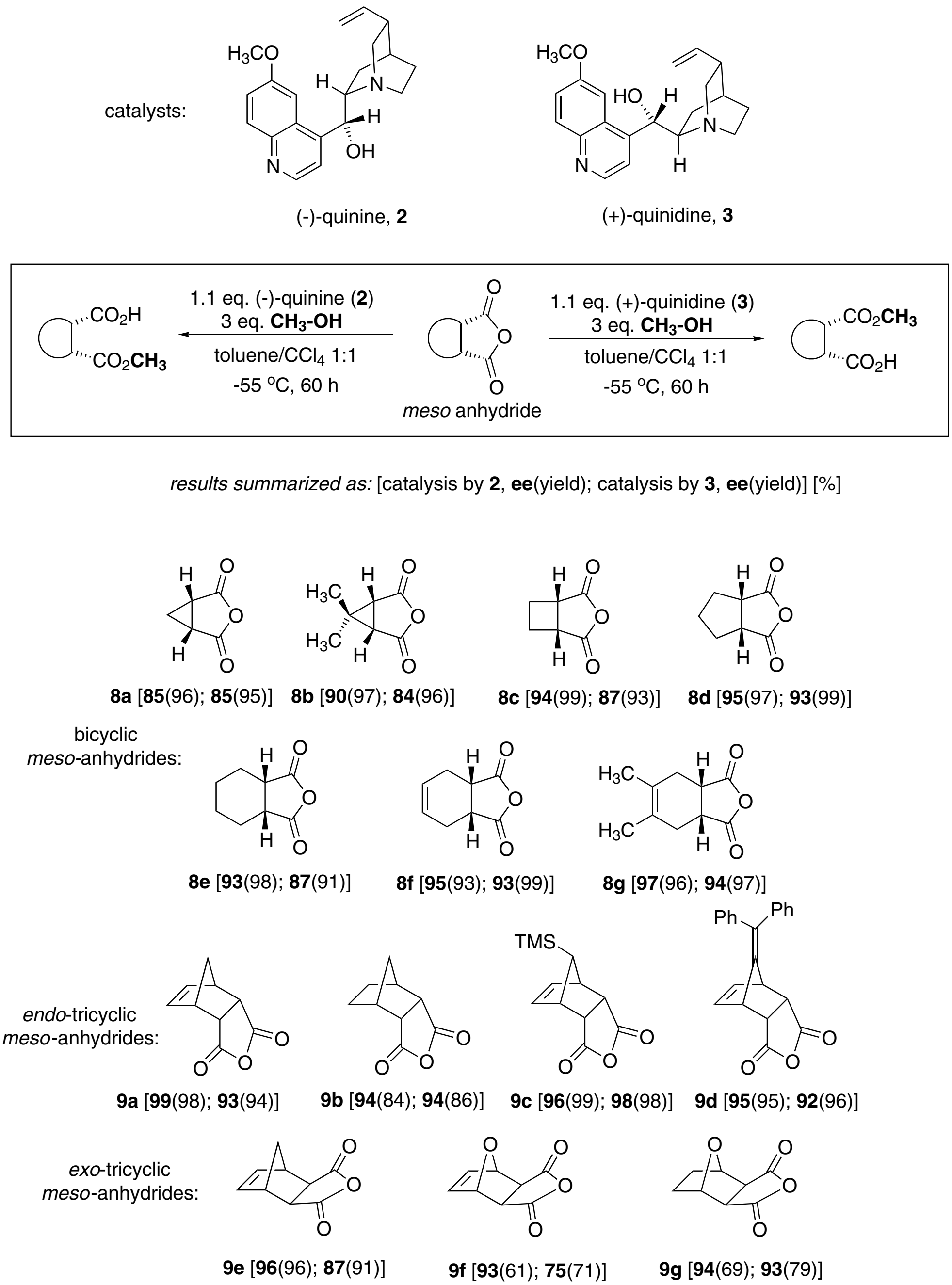
Dynamic kinetic resolution of racemic anhydrides: In this reaction catalyst **A** effects the conversion of one substrate enantiomer to the product monoester while the reactive substrate enantiomer is continuously regenerated by racemization of the "unreactive" substrate enantiomer. A second catalyst (**B**, Scheme 13.1, bottom right) is used to effect the latter racemization. In an ideal dynamic kinetic resolution (DKR) 100% of one product enantiomer is generated from the racemic substrate; this makes this type of reaction highly desirable. This section covers in particular the DKR of α-hydroxy acid *O*-carboxy anhydrides (X = O) and of α-amino acid *N*-carboxy anhydrides (X = NR). In these reactions attack of the alcohol nucleophile occurs exclusively – as indicated in Scheme 13.1 (bottom right) – at the more electrophilic carbonyl group, and both the alcoholysis and racemization steps are effected by the same catalyst (**A** = **B**). The related dynamic kinetic resolution of azlactones by ring-opening with alcohols is covered in Section 13.6.

13.1.1
Desymmetrization of Prochiral Cyclic Anhydrides

In the mid-1980s Oda et al. reported that of a series of alkaloids screened for catalytic desymmetrization of cyclic *meso*-anhydrides with methanol, (+)-cinchonine (**1**) performed best [4–6]. As shown in Scheme 13.2, 10 mol% of this catalyst was



Scheme 13.2


catalysts:
(-)-quinine, 2
(+)-quinidine, 3
1.1 eq. (-)-quinine (2)
3 eq. CH3-OH
toluene/CCl4 1:1
-55 °C, 60 h
meso anhydride
1.1 eq. (+)-quinidine (3)
3 eq. CH3-OH
toluene/CCl4 1:1
-55 °C, 60 h
results summarized as: [catalysis by 2, ee(yield); catalysis by 3, ee(yield)] [%]
8a [85(96); 85(95)]
8b [90(97); 84(96)]
8c [94(99); 87(93)]
8d [95(97); 93(99)]
bicyclic meso-anhydrides:
8e [93(98); 87(91)]
8f [95(93); 93(99)]
8g [97(96); 94(97)]
endo-tricyclic meso-anhydrides:
9a [99(98); 93(94)]
9b [94(84); 94(86)]
9c [96(99); 98(98)]
9d [95(95); 92(96)]
exo-tricyclic meso-anhydrides:
9e [96(96); 87(91)]
9f [93(61); 75(71)]
9g [94(69); 93(79)]

Scheme 13.3

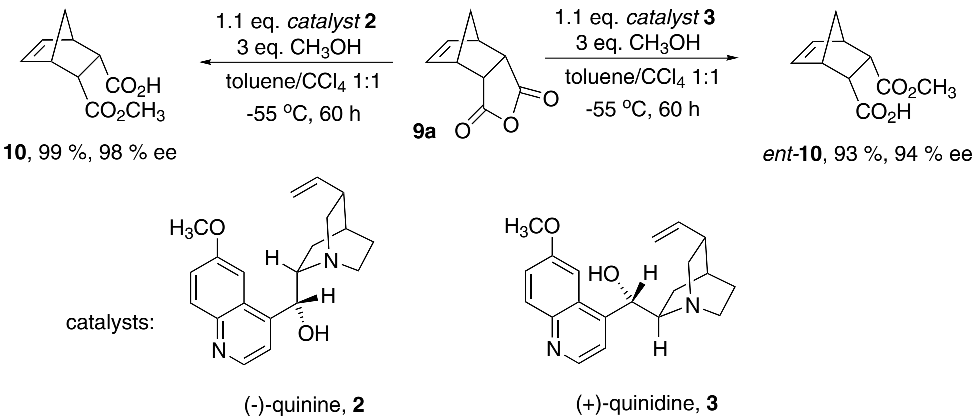
sufficient to convert *cis*-2,4-dimethylglutaric anhydride (**4**) to its methyl hemi-ester **5** in almost quantitative yield and 70% ee. By using a variety of polymer-supported quinine derivatives Oda et al. achieved up to 33% ee in the desymmetrization of the glutaric anhydride **4** (Scheme 13.2) [6].

Related studies on *meso* tricyclic anhydrides were published in 1988 and 1990 by Aitken et al. [7, 8]. Their best result was achieved in the methanolysis of the tetracyclic anhydride **6** with (−)-quinine (**2**) as catalyst (Scheme 13.2; 57% yield of the lactone ester **7** with 76% ee). The enantiomeric purity of the tricyclic lactone-ester **7** could be increased significantly (≥ 99% ee) by subsequent recrystallization in the presence of (−)-quinine (**2**).

A very efficient and practical process for desymmetrization of *meso*-anhydrides was reported by Bolm et al. in 1999 and in subsequent publications (Scheme 13.3) [9, 10]. In their approach, which is a further development and improvement in the use of alkaloids as catalysts, (−)-quinine (**2**) or (+)-quinidine (**3**) in this case, low reaction temperature and solvent optimization proved crucial to achieving optimum enantioselectivity. Under their conditions methanolysis of several meso anhydrides (**8a–g**, **9a–g**, Scheme 13.3) can be achieved in good yields and with excellent enantiomeric excesses in the presence of equimolar amounts of the inexpensive and readily available alkaloids **2** and **3** [9, 10].

As exemplified in Scheme 13.4, attack of the nucleophile methanol occurs uniformly at one or the other of the two enantiotopic carbonyl groups of the *meso*-anhydride (affording the hemi-esters **10** and *ent*-**10**, respectively), depending on whether (−)-quinine (**2**) or (+)-quinidine (**3**) is employed as catalyst.

The desymmetrizations performed by Bolm et al. were usually conducted at −55 °C in a mixture of toluene and carbon tetrachloride. For best results, slightly over-stoichiometric amounts of the alkaloids (1.1 equiv.) were used. The amount of catalyst could, however, be reduced to 10 mol% when a stoichiometric amount of the achiral and non-nucleophilic base 1,2,2,6,6-pentamethylpiperidine was added [10]. Further improvement resulted from systematic screening of alcohol nucleo-



Scheme 13.4

philes. Benzyl alcohol was found to afford consistently high enantiomeric excesses with both (−)-quinine (**2**) and (+)-quinidine (**3**) as catalysts (Scheme 13.5) [11]. In addition, the crystallinity of many of benzyl mono-esters is advantageous in terms of product purification. With benzyl alcohol as the nucleophile the desymmetrization reaction can be performed in pure toluene as solvent (i.e. without carbon tetrachloride) with identical or even better yields and ee [11].

The mono-esters thus prepared have been used by Bolm et al. for selective synthesis of two-stranded peptidic structures with parallel arrangement of the peptide strands [12]. They also enable easy access to unnatural *β*-amino acids in enantiomerically pure form. The latter reaction sequence involves conversion of the carboxyl group to an acyl azide and subsequent Curtius degradation [11, 13, 14].

Deng et al. investigated the potential of modified cinchona alkaloids – in particular those usually employed as ligands in the Sharpless asymmetric dihydroxylation – in the alcoholytic desymmetrization of cyclic anhydrides (Scheme 13.6) [15]. It was found that the anthraquinone-bridged dimers of dihydroquinidine, $(DHQD)_2AQN$, **11**, and dihydroquinine, $(DHQ)_2AQN$, **12**, provide excellent enantiomeric excesses (up to 98%) in the methanolysis of several anhydrides at catalyst loadings of only 5–30 mol% (Scheme 13.6) [15]. Deng et al. later applied their desymmetrization method to the formal catalytic asymmetric synthesis of (+)-biotin [16].

The non-alkaloid derived organocatalysts **13a**–**e** – readily accessible from proline and hydroxyproline, respectively – were reported by Uozomi et al. (Scheme 13.7) [17]. Of the five compounds, **13b** and **13e** performed best. In the presence of 100 mol% **13e**, the methanolytic desymmetrization of cyclic meso anhydrides was found to proceed with up to 89% ee.

A related enantiotopos-differentiating desymmetrization, the CBS-reduction of cyclic meso imides, was reported in 1997 by Hiemstra et al. [18].

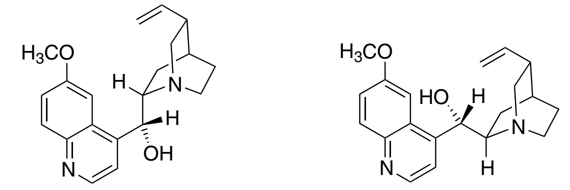
13.1.2
Kinetic Resolution of Chiral, Racemic Anhydrides

No examples of simple organocatalytic kinetic resolution of dicarboxylic acid anhydrides, e.g. by alcoholysis (Scheme 13.1, middle, $X = CR_2$) seem to have been reported. This type of transformation requires that one anhydride enantiomer remains unchanged while the other is transformed to a mono-ester. Nucleophilic catalysts such as cinchona alkaloids have been shown to effect parallel kinetic resolution, that is, the two enantiomers of the anhydride are converted to regioisomeric esters. This type of transformation is therefore discussed in Section 13.1.3.

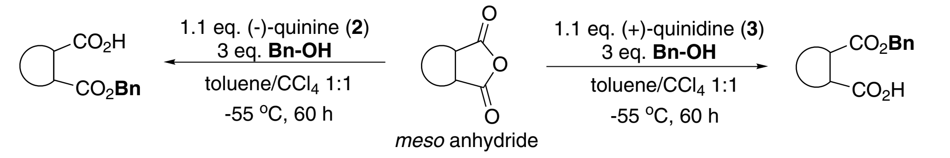
13.1.2.1 Kinetic Resolution of 1,3-Dioxolane-2,4-diones (α-Hydroxy Acid *O*-Carboxy Anhydrides)

Deng and Tang reported in 2002 that the 5-alkyl 1,3-dioxolane-2,4-diones *rac*-**15** shown in Scheme 13.8 undergo kinetic resolution in the presence of alcohols and dimeric cinchona alkaloids such as $(DHQD)_2AQN$ **11** [19]. In a first step, the racemic α-hydroxy carboxylic acids *rac*-**14** were reacted with diphosgene to afford the

catalysts:

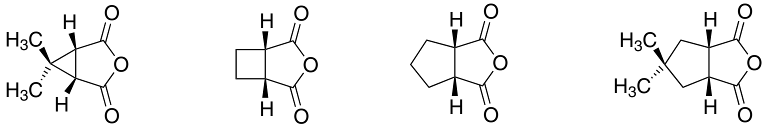


(-)-quinine, **2** (+)-quinidine, **3**

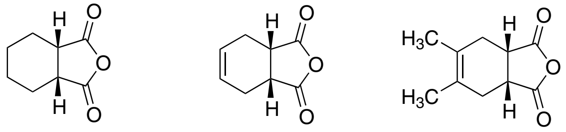


results summarized as:
top line: conditions as above, toluene/CCl_4-mixture [catalysis by **2**, **ee**(yield); catalysis by **3**, **ee**(yield)] [%]
bottom line: conditions as above, but pure toluene [catalysis by **2**, **ee**(yield); catalysis by **3**, **ee**(yield)] [%]

bicyclic *meso*-anhydrides:

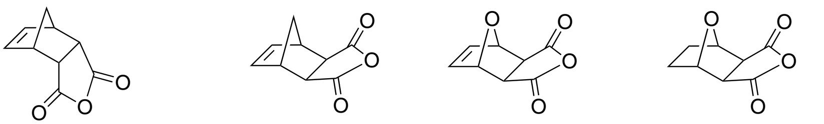


8b [**88**(94); **92**(95)] [**86**(86); **90**(93)]
8c [**90**(85); **93**(90)] [**90**(90); **95**(94)]
8d [**95**(89); **97**(93)] [**94**(90); **95**(94)]
8h [**95**(83); **97**(78)]



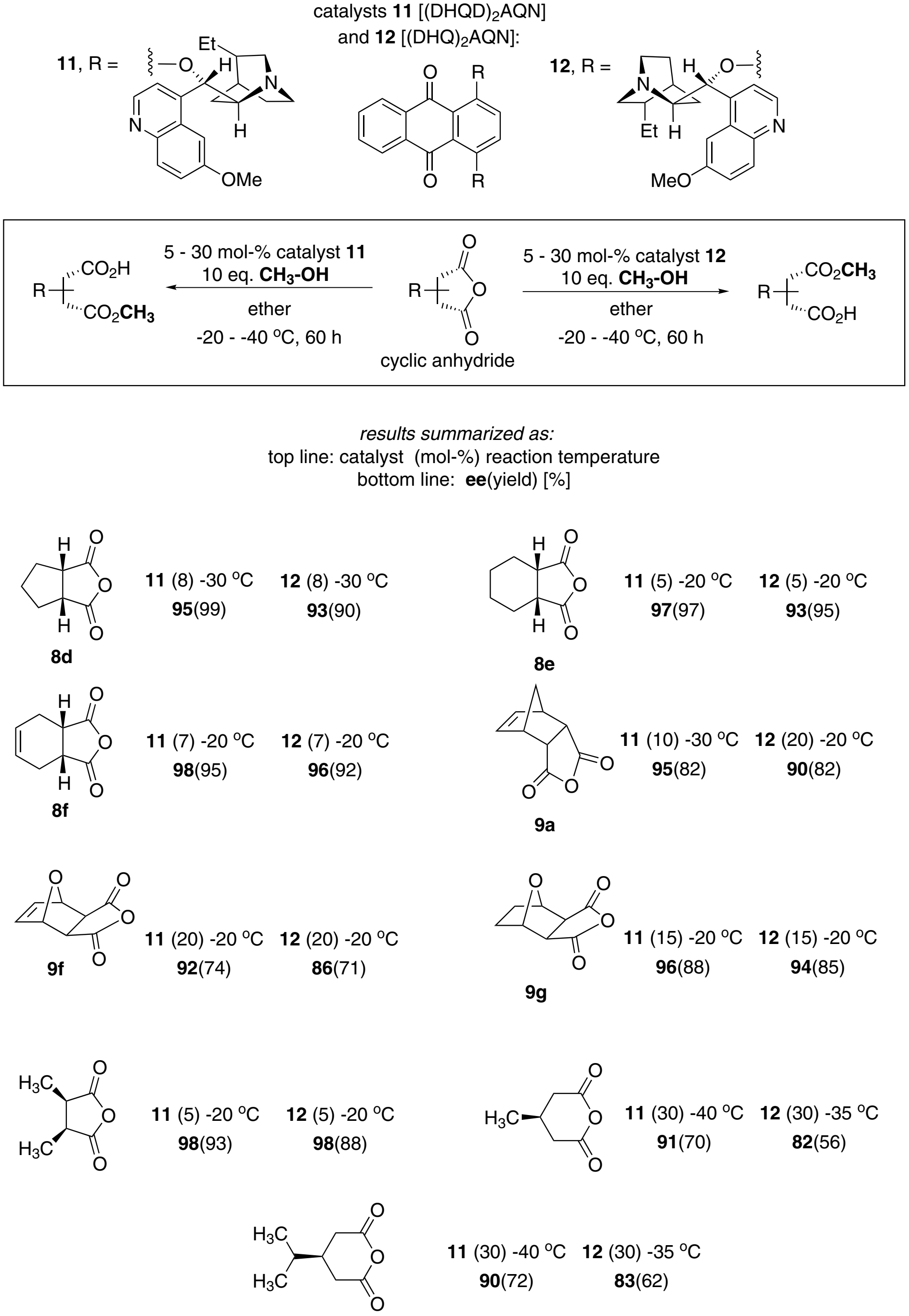
8e [**93**(84); **95**(88)] [**93**(86); **96**(85)]
8f [**95**(84); **94**(84)]
8g [**97**(87); **98**(88)]

endo-tricyclic *meso* anhydride: *exo*-tricyclic *meso* anhydrides:



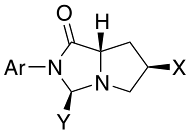
9a [**96**(93); **97**(92)] [**95**(90); **96**(85)]
9e [**92**(81); **96**(95)]
9f [**94**(77); **99**(84)]
9g [**90**(85); **96**(79)]

Scheme 13.5

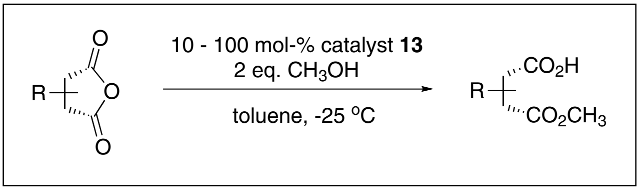

catalysts 11 [(DHQD)2AQN]
and 12 [(DHQ)2AQN]:
11, R =
12, R =
Et
H
N
OMe
MeO
O
R
5 - 30 mol-% catalyst 11
10 eq. CH3-OH
ether
-20 - -40 °C, 60 h
CO2H
CO2CH3
cyclic anhydride
5 - 30 mol-% catalyst 12
10 eq. CH3-OH
ether
-20 - -40 °C, 60 h
results summarized as:
top line: catalyst (mol-%) reaction temperature
bottom line: ee(yield) [%]
8d
11 (8) -30 °C 12 (8) -30 °C
95(99) 93(90)
8e
11 (5) -20 °C 12 (5) -20 °C
97(97) 93(95)
8f
11 (7) -20 °C 12 (7) -20 °C
98(95) 96(92)
9a
11 (10) -30 °C 12 (20) -20 °C
95(82) 90(82)
9f
11 (20) -20 °C 12 (20) -20 °C
92(74) 86(71)
9g
11 (15) -20 °C 12 (15) -20 °C
96(88) 94(85)
H3C
11 (5) -20 °C 12 (5) -20 °C
98(93) 98(88)
11 (30) -40 °C 12 (30) -35 °C
91(70) 82(56)
11 (30) -40 °C 12 (30) -35 °C
90(72) 83(62)

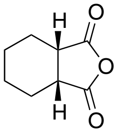
Scheme 13.6

catalysts **13a-e**:



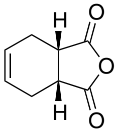
13a: Ar = Ph; X = Y H
13b: Ar = Ph, X = OH; Y = H
13c: Ar = Ph; X = OTBDMS; Y = H
13d: Ar = Ph; X = OH; Y = Ph
13e: Ar = 4-*n*-C_8H_{17}-C_6H_4; X = OH; Y = H





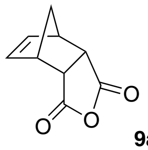
8e

13b (10 mol-%) : 40 %, 65 % ee
13e (10 mol-%): 33 %, 65 % ee
13e (100 mol-%): 72 %, 89 % ee



8f

13e (100 mol-%): 85 % ee



9a

13e (100 mol-%): 82 % ee

Scheme 13.7

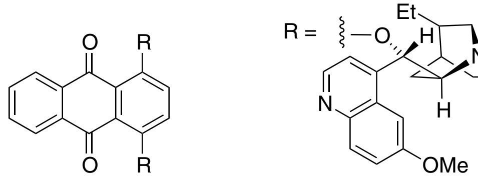
1,3-dioxolane-2,4-diones *rac*-**15**. Treatment of the latter with ethanol or allyl alcohol in the presence of 10 mol% catalyst **11** resulted in the enantioselective conversion (selectivity factors up to 133) of (*R*)-**15** to the ester (*R*)-**16**. By hydrolysis of the crude reaction mixture, the remaining anhydride (*S*)-**15** was converted back to the α-hydroxy acid (*S*)-**14**. The mixture of the acid (*S*)-**14** and the ester (*R*)-**16** was then easily separated by extraction.

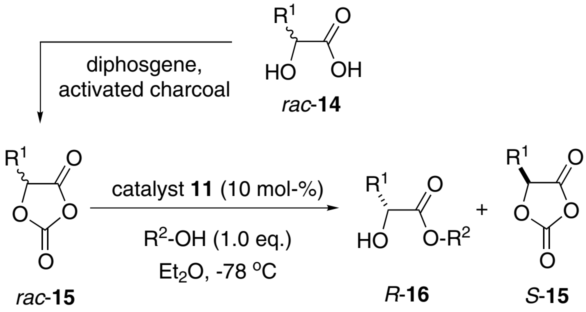
When 5-*aryl* 1,3-dioxolane-2,4-diols were employed instead of the 5-*alkyl* substituted substrates *rac*-**15**, additional racemization of the anhydrides occurred, resulting in overall dynamic kinetic resolution. This reaction is covered in Section 13.1.4.1 [19].

13.1.2.2 Kinetic Resolution of *N*-Urethane-protected Amino Acid *N*-Carboxy Anhydrides

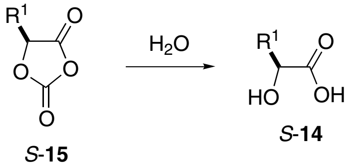
Deng et al. reported in 2001 that a wide variety of *N*-urethane-protected *N*-carboxy anhydrides such as, for example, *rac*-**18** shown in Scheme 13.9 undergo kinetic resolution when treated at low temperature with alcohols in the presence of dimeric cinchona alkaloids such as $(DHDQ)_2AQN$, **11** [20]. The *N*-carboxy anhydrides *rac*-**18** were prepared from the racemic amino acids *rac*-**17** by a two-step procedure involving cyclization with diphosgene and subsequent *N*-protection with, e.g., Cbz or Fmoc. The kinetic resolution of *rac*-**18** proceeded with excellent

catalyst **11** [$(DHQD)_2AQN$]:





R^1	R^2	ee (yield) [%] *S*-**14**	ee (yield) [%] *R*-**16**	*s*
$PhCH_2$	Et	95 (39)	96 (47)	133
$PhCH_2CH_2$	Et	85 (40)	93 (46)	67
$CH_3(CH_2)_3$	Et	95 (36)	92 (46)	57
$(CH_3)_2CH$	allyl	95 (32)	90 (48)	49

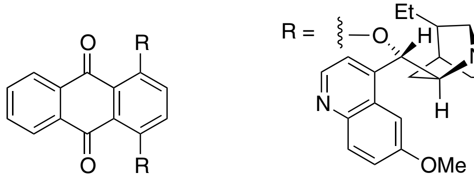


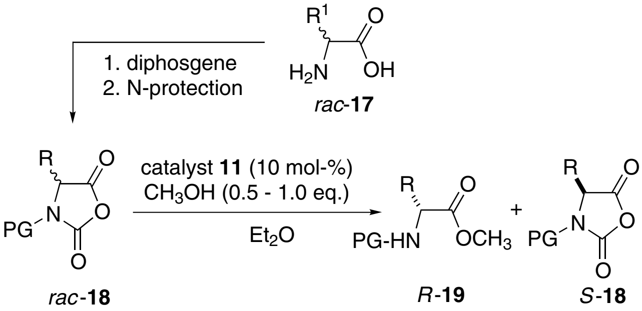
Scheme 13.8

enantioselection (selectivity factors up to 170), affording the methyl esters (*R*)-**19** and the unchanged anhydride (*S*)-**18**. As for the *O*-carboxy anhydrides discussed above, hydrolysis of the crude reaction mixture converted the remaining anhydride (*S*)-**18** to the *N*-protected α-amino acid (*S*)-**20** (Scheme 13.9). The mixture of the (acidic) amino acid (*S*)-**20**, the (neutral) ester (*R*)-**19**, and the (basic) catalyst **11** was then easily separated by extraction.

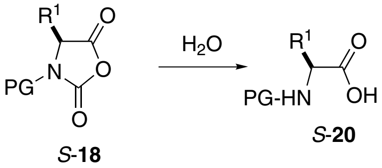
Analogous treatment of the aryl *N*-carboxy anhydrides *rac*-**18** at higher temperature induces simultaneous racemization of the starting material. As a conse-

catalyst **11** [$(DHQD)_2AQN$]:





R	PG	Temp. [°C]	ee (yield) [%] *S*-**20**	ee (yield) [%] *R*-**19**	*s*
Ph	Cbz	-78	84 (46)	97 (45)	170
2-thienyl-CH_2	Cbz	-78	95 (47)	94 (49)	115
$PhCH_2$	Cbz	-60	98 (48)	93 (48)	114
$PhCH_2$	Fmoc	-78	96 (47)	92 (50)	93
4-F-Ph	Cbz	-78	93 (42)	92 (48)	79
$CH_3(CH_2)_5$	Cbz	-60	94 (42)	91 (49)	78
$BnOCH_2$	Cbz	-78	96 (44)	89 (49)	69

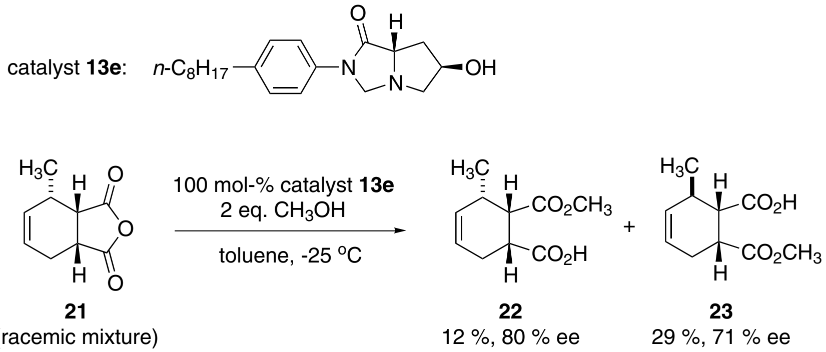


Scheme 13.9

quence, kinetic resolution of the *N*-carboxy anhydrides becomes *dynamic* [21]. Similarly, alkyl *N*-carboxy anhydrides of general structure **18** are amenable to dynamic kinetic resolution if more strongly electron-withdrawing protecting groups are present on the nitrogen atom [22]. Both processes are covered in Section 13.1.4.

13.1.3
Parallel Kinetic Resolution of Chiral, Racemic Anhydrides

In 2001 Uozomi et al. reported that the (3-methyl)tetrahydrophthalic anhydride *rac*-**21** undergoes parallel kinetic resolution when treated with methanol in the presence of the hydroxy proline derivative **13e** (Scheme 13.10) [17]. The resulting esters **22** and **23** were formed with up to 80% ee, albeit at chemical yields of 12% and 29%, respectively.



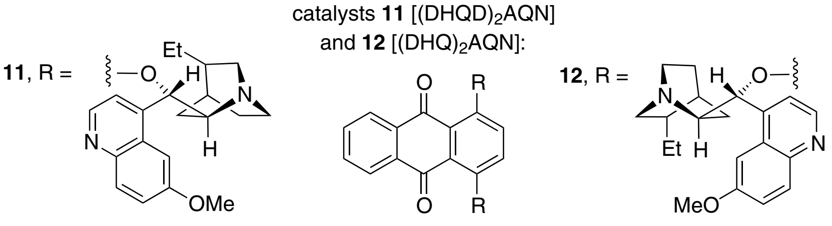
Scheme 13.10

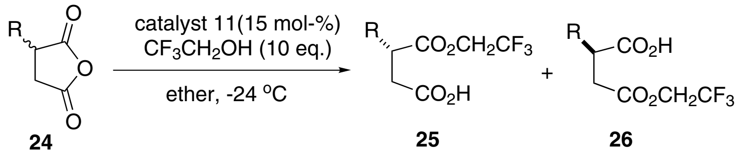
In the same year Deng and Chen reported the highly efficient parallel kinetic resolution of 2-alkyl and 2-aryl succinic anhydrides (**24**) catalyzed by dimeric cinchona alkaloids such as $(DHDQ)_2AQN$ (**11**) or $(DHQ)_2AQN$ (**12**) (Scheme 13.11) [23]. In this study it was found that 2,2,2-trifluoroethanol as the nucleophile provides the best enantioselectivity. This result is in contrast with the observation by Bolm et al. that 2,2,2-trifluoroethanol – as the only alcohol nucleophile – affords racemic products in the alkaloid-catalyzed desymmetrization of meso anhydrides [11].

With the alkyl-substituted succinic anhydrides **24a–d**, the resulting mono-esters **25** and **26** can be separated by conventional column chromatography on silica. The same is true for the aryl butyrolactones **27** and **28**, obtained by reduction/cyclization of the mono-esters **25**, **26** resulting from the resolution of the aryl-substituted succinic anhydrides **24e–g**. The lactone **27** thus prepared from **24g** has served before as an intermediate in the enantioselective synthesis of the GABA receptor antagonist baclofen [24]. It should be noted that the selectivity obtained in the parallel kinetic resolution of **24g** corresponds to a selectivity factor of at least 112 in conventional kinetic resolution [23].

13.1.4
Dynamic Kinetic Resolution of Racemic Anhydrides

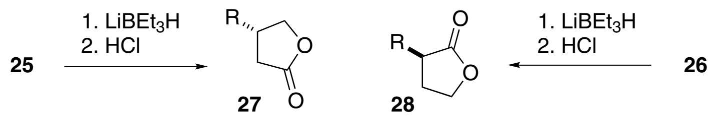
No examples of organocatalytic dynamic kinetic resolution of dicarboxylic acid anhydrides, e.g. by alcoholysis (Scheme 13.1, bottom right, $X = CR_2$), seem to have been reported.





	R	ee (yield) [%]			
		25	**26**	**27**	**28**
24a	CH_3	93 (36)	80 (41)	---	---
24b	CH_3CH_2	91 (38)	70 (50)	---	---
24c	*n*-octyl	98 (38)	66 (41)	---	---
24d	allyl	96 (40)	82 (49)	---	---
24e	Ph	95	87	95 (44)	82 (32)
24f	3-MeO-Ph	96	83	95 (45)	83 (30)
24g	4-Cl-Ph	96	76	96 (44)	63 (29)

For R = Ph, 3-MeO-Ph or 4-Cl-Ph:

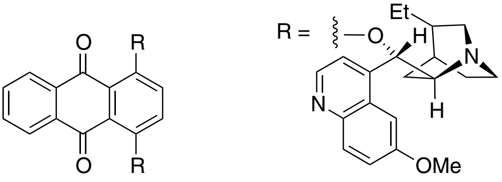


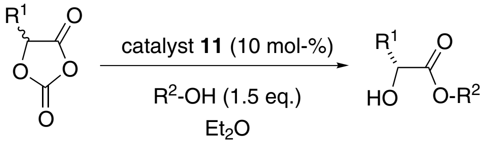
Scheme 13.11

13.1.4.1 Dynamic Kinetic Resolution of 1,3-Dioxolane-2,4-diones (α-Hydroxy acid *O*-Carboxy Anhydrides)

Scheme 13.8 summarized kinetic resolution of the 5-*alkyl*-1,3-dixolane-2,4-diones *rac*-**15** by alcoholysis in the presence of the dimeric cinchona alkaloid catalyst **11**, $(DHQD)_2AQN$, as reported by Tang and Deng [19]. These authors observed that the related 5-*aryl*-1,3-dioxolane-2,4-diones **29** (Scheme 13.12) underwent rapid racemization under the reaction conditions used, thus enabling dynamic kinetic resolution. This difference in reactivity was attributed to the higher acidity of the α-CH

catalyst **11** [$(DHQD)_2AQN$]:





rac-**29** *R*-**30**

R^1	R^2	Temp. [°C]	ee (yield) [%] *R*-**30**
Ph	Et	-78	95 (71)
4-Br-Ph	Et	-78	96 (80)
4-CF_3-Ph	Et	-78	93 (85)
3,4-F_2-Ph	Et	-78	94 (65)
4-*i*-Pr-Ph	Et	-78	91 (68)
1-naphthyl	*n*-Pr	-40	91 (74)
2-Cl-Ph	Et	-60	62 (66)

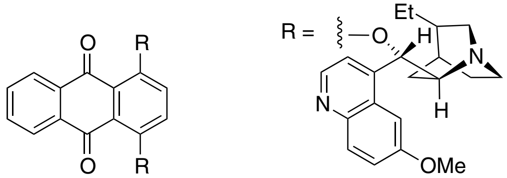
Scheme 13.12

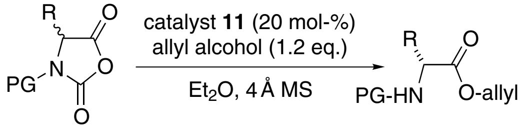
in the aryl-substituted anhydrides *rac*-**29**. Clearly, configurational stability of the resulting esters (*R*)-**30** must sufficiently be retained for efficient dynamic kinetic resolution. As shown in Scheme 13.12, enantiomerically highly enriched (ee up to 96%) α-hydroxy acid mono-esters **30** were obtained by this method in yields of up to 85% starting from the corresponding racemic *O*-carboxy anhydrides [19].

13.1.4.2 Dynamic Kinetic Resolution of *N*-protected Amino Acid *N*-Carboxy Anhydrides

Scheme 13.9 summarized kinetic resolution of *N*-urethane protected *N*-carboxy anhydrides *rac*-**18** by methanolysis in the presence of the dimeric cinchona alkaloid catalyst **11**, $(DHQD)_2AQN$, as reported by Deng et al. [20]. These kinetic resolutions were typically conducted at low temperature – from −78 to −60 °C. Deng et al. later observed that if the reaction temperature was increased racemization of the starting aryl *N*-carboxy anhydrides *rac*-**18** becomes sufficiently rapid to enable a dynamic kinetic resolution [21]. Configurational stability of the product esters

catalyst **11** [$(DHQD)_2AQN$]:





rac-**18**   *R*-**19**

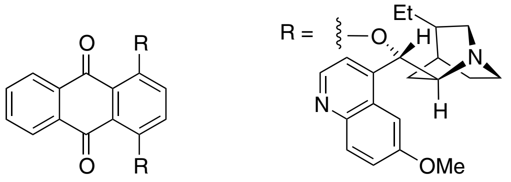
R	PG	Temp. [°C]	ee (yield) [%] *R*-**19**
Ph	Cbz	23	91 (97)
Ph	Fmoc	23	90 (98)
4-F-Ph	Cbz	23	90 (96)
4-Cl-Ph	Cbz	23	92 (97)
4-CF_3-Ph	Cbz	23	90 (95)
2-thienyl	Cbz	23	92 (93)
3-thienyl	Cbz	-30	91 (95)
2-furyl	Cbz	23	91 (98)
2-(4-methylfuryl)	Cbz	23	93 (97)
3-(N-tosylindolyl)	Cbz	0	90 (95)

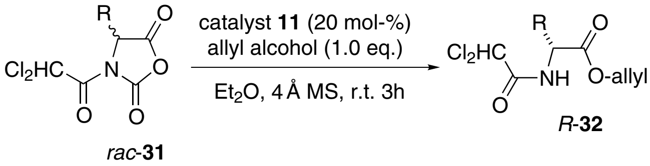
Scheme 13.13

(*R*)-**19** under the reaction conditions is a pre-requisite that is again fulfilled in this process. As shown in Scheme 13.13, enantiomeric excesses > 90% and almost quantitative yields were achieved for several aryl *N*-carboxy anhydrides. In these examples allyl alcohol was used as the nucleophile. The corresponding amino acids can be liberated quantitatively and with unchanged ee from the esters (*R*)-**19** by Pd-catalyzed deallylation, using morpholine as the nucleophile (Scheme 13.13) [25].

Urethane-protected *alkyl N*-carboxy anhydrides do not racemize effectively under the conditions established for the dynamic kinetic resolution of *aryl N*-carboxy anhydrides. As for the 1,3-dioxolane-2,4-diones *rac*-**29** (*aryl*, Scheme 13.12) and *rac*-**15** (*alkyl*, Scheme 13.8) this different reactivity can be attributed to the lower acidity of the α-CH in the alkyl-substituted anhydrides. To overcome this hurdle Deng and

catalyst **11** [$(DHQD)_2AQN$]:





R	ee (yield) [%] *R*-**32**
Ph-CH_2	66 (81)
4-F-Ph-CH_2	67 (82)
4-Cl-Ph-CH_2	68 (75)
4-Br-Ph-CH_2	70 (82)
(2-thienyl)methyl	75 (87)
Ph-CH_2CH_2	59 (77)

Scheme 13.14

Hang exchanged the urethane *N*-protecting group in the *N*-carboxy anhydrides by more electron withdrawing groups [22]. Of the different protecting groups tested, dichloroacetyl proved best. As summarized in Scheme 13.14, several *N*-carboxy anhydrides *rac*-**31** were converted to the allylic esters (*R*)-**32** with enantiomeric excesses up to 75%. For the (2-thienyl)methylglycine derivative the ee of the product *N*-dichloroacetyl allyl ester could be increased to >99% by recrystallization (53% yield after recrystallization) [22].

Conclusions

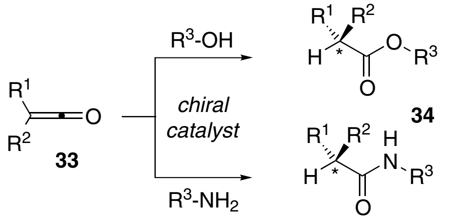
The field of organocatalytic enantioselective anhydride transformations has seen tremendous progress during recent years. For example, the alcoholytic desymmetrization of meso anhydrides, effected by stoichiometric quantities of inexpensive and readily available cinchona alkaloids, has been developed to a very practical level, and several applications, e.g. for the synthesis of enantiomerically pure

β-amino acids, have resulted. An alternative alcoholytic anhydride desymmetrization requiring only sub-stoichiometric (5–30 mol%) quantities of catalyst was developed as well. In this process dimeric cinchona alkaloid derivatives, originally designed as ligands for the Sharpless dihydroxylation and commercially available, were employed. These materials were also found to be very selective for parallel kinetic resolution of racemic anhydrides, for example 4-alkyl and aryl succinic anhydrides, giving rise to regioisomeric mono-esters.

Quite remarkable progress has also been achieved in enantioselective transformation of cyclic anhydrides derived from α-hydroxy and α-amino carboxylic acids. By careful choice of the reaction conditions, *dynamic* kinetic resolution by alcoholysis has become reality for a broad range of substrates. Again, the above mentioned dimeric cinchona alkaloids were the catalysts of choice. In other words, organocatalytic methods are now available for high-yielding conversion of racemic α-hydroxy and α-amino acids to their enantiomerically pure esters. If desired, the latter esters can be converted back to the parent – but enantiomerically pure – acids by subsequent ester cleavage.

13.2 Additions to Prochiral Ketenes

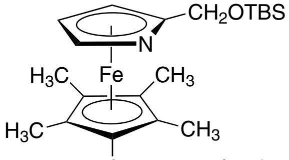
Attempts to convert prochiral ketenes such an **33** (Scheme 13.15) into enantioenriched derivatives of α-chiral carboxylic acids (**34**, Scheme 13.15) are among the earliest examples of asymmetric nucleophilic catalysis in general.



Scheme 13.15

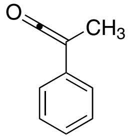
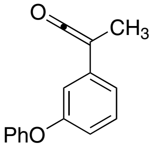
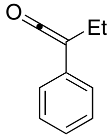
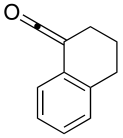
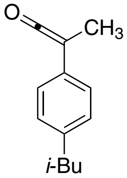
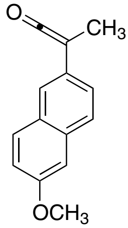
Pioneering work by Pracejus et al. in the 1960s, using alkaloids as catalysts, afforded quite remarkable 76% ee in the addition of methanol to phenylmethylketene [26–29]. In 1999 Fu et al. reported that of various planar-chiral ferrocene derivatives tried, the azaferrocene **35** performed best in the asymmetric addition of methanol to several prochiral ketenes [30, 31]. In the presence of 10 mol% catalyst **35** (and 12 mol% 2,6-di-*tert*-butylpyridinium triflate as proton-transfer agent), up to 80% ee was achieved (Scheme 13.16).

Pracejus et al. also demonstrated that diastereoselective addition of chiral amines to prochiral ketenes is possible [28, 32, 33] whereas attempts to *catalytically* produce enantiomerically enriched amides were frustrated by rapid uncatalyzed ad-



catalyst **35**

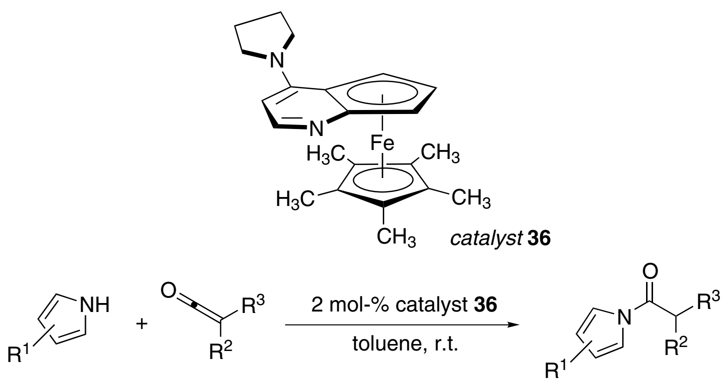
CH_3OH + ketene → (10 mol-% catalyst **35**, 12 mol-% 2,6-di-*tert*-butylpyridinium triflate; toluene, -78 °C) → enantiomerically enriched methyl ester

Substrate ketene	Methyl ester ee [%]	Methyl ester yield [%]	Substrate ketene	Methyl ester ee [%]	Methyl ester yield [%]
	77	87		74	96
	68	92		80	97
	77	88		75	80

Scheme 13.16

dition of the (achiral) amines to the ketenes. Fu et al., however, have recently demonstrated the possibility of catalytic asymmetric addition of less reactive *N*-nucleophiles, for example pyrroles, to aryl alkyl ketenes [34]. In the presence of 2 mol% of the planar-chiral DMAP derivative **36**, up to 98% ee was achieved (Scheme 13.17).

As shown in Scheme 13.17, 2-cyanopyrrole, in particular, adds to a variety of ketenes with quite high enantioselectivity. Fu et al. also demonstrated several transformations of the initially formed *N*-acyl 2-cyanopyrroles into enantiomerically pure secondary products, for example α-chiral aldehydes, esters, and amides (Scheme 13.18) [34].



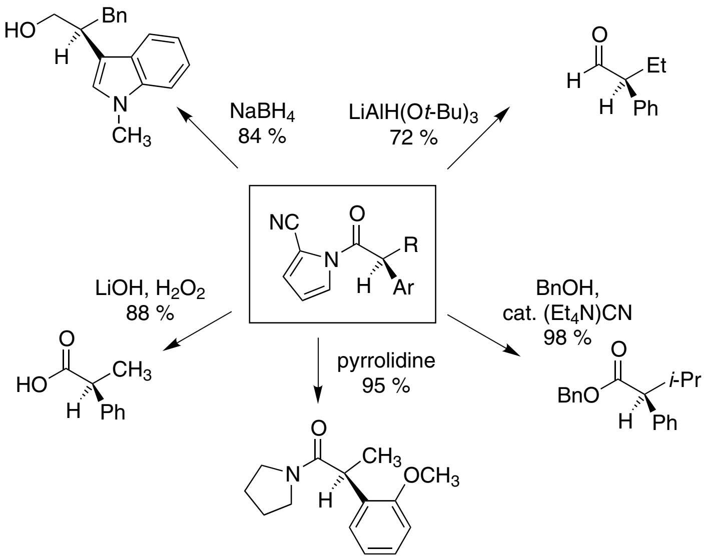
R^1	R^2	R^3	ee [%]	Yield [%]
H	Ph	Et	42	n.r.
2-Et	Ph	Et	0	n.r.
2-NO_2	Ph	Et	21	n.r.
2-Ac	Ph	Et	78	n.r.
2-CN	Ph	Et	91	n.r.
3,4-di-carboethoxy	Ph	Et	63	n.r.
Indole	Ph	Et	49	n.r.
2-CN	Ph	Et	90	93
2-CN	Ph	Me	81	91
2-CN	Ph	*i*-Pr	95	96
2-CN	Ph	*t*-Bu	81	90
2-CN	*o*-tolyl	Et	98	85
2-CN	*o*-anisyl	Me	94	94
2-CN	3-(*N*-methyl-indolyl)	Bn	86	80

n.r.: not reported

Scheme 13.17

Conclusions

The alkaloid-catalyzed addition of alcohols to prochiral ketenes is one of the very first examples of catalytic asymmetric synthesis. In pioneering work by Pracejus in the 1960s quite remarkable 76% ee was achieved and it was not until 1999 that substantial improvement of enantioselectivity in catalytic asymmetric addition of *O*- and *N*-nucleophiles to prochiral ketenes was reported. In particular, the chiral

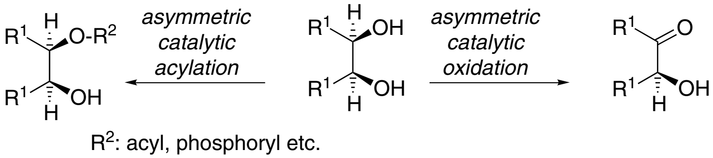


Scheme 13.18

azaferrocenes and DMAP derivatives reported by Fu currently perform best. Quite useful enantioselectivity (up to 98% ee) has been achieved in the addition of pyrrole derivatives to prochiral aryl alkyl ketenes.

13.3 Desymmetrization of *meso*-Diols

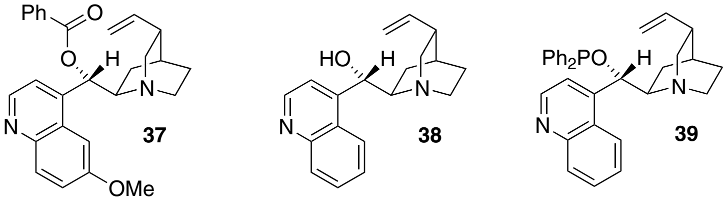
The desymmetrization of meso diols requires selective chemical transformation of one of the two enantiotopic hydroxyl functions. Among other possibilities this transformation can consist in acylation or – less commonly – oxidation to a ketone (Scheme 13.19). It should be noted that the enantiomeric purity of the initial reaction products can be "upgraded" by subsequent conversion of the unwanted enantiomer into the diacylated compound (or diketone), i.e. by subsequent kinetic resolution.

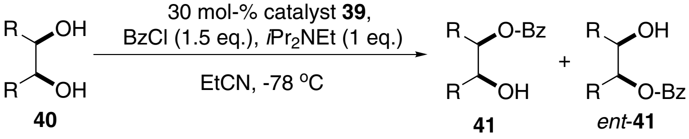


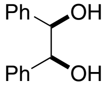
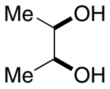
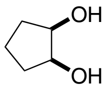
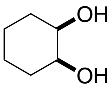
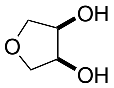
Scheme 13.19

13.3.1
Desymmetrization of *meso*-Diols by Acylation

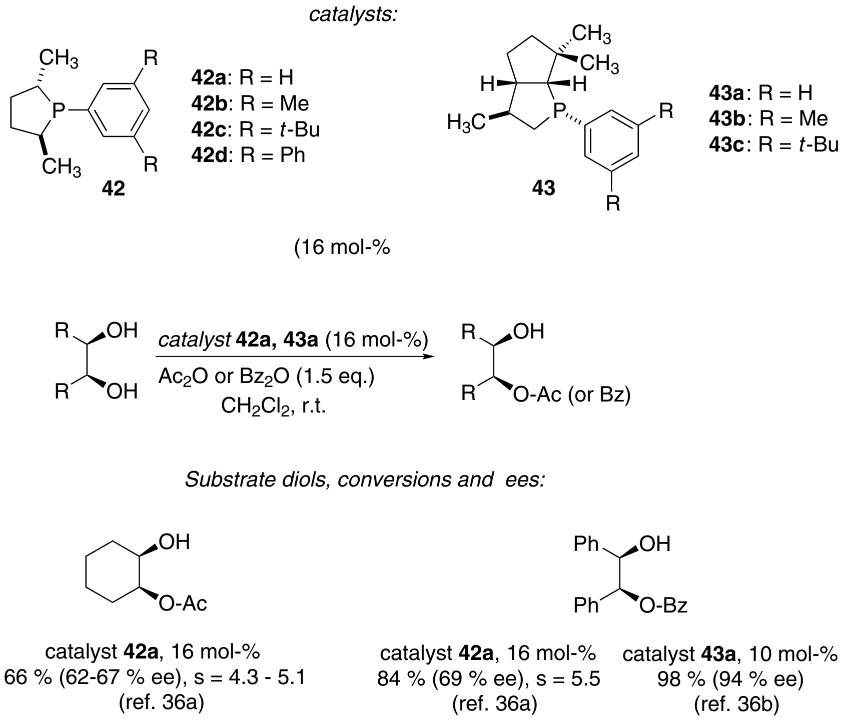
In an early example of the desymmetrization of *meso*-diols by acylation Duhamel and Herman employed benzoyl chloride and *O*-benzoylquinidine **37** in twofold excess over the meso substrate *cis*-2-cyclopentene-1,4-diol [35a]. In this example, the mono-benzoate was obtained with up to 47% ee, albeit at low chemical yield (10%). A truly catalytic reaction based on the cinchonine phosphinite **39**, and providing significantly improved enantioselection, was recently achieved by Fujimoto et al. (Scheme 13.20) [35b]. As shown in Scheme 13.20, several *meso*-diols **40** were





meso-diol	Major product enantiomer	Yield [%]	ee [%]
	*ent*-**41**	98	91
	**41**	99	86
	**41**	80	93
	**41**	85	94
	n.d.	80	76

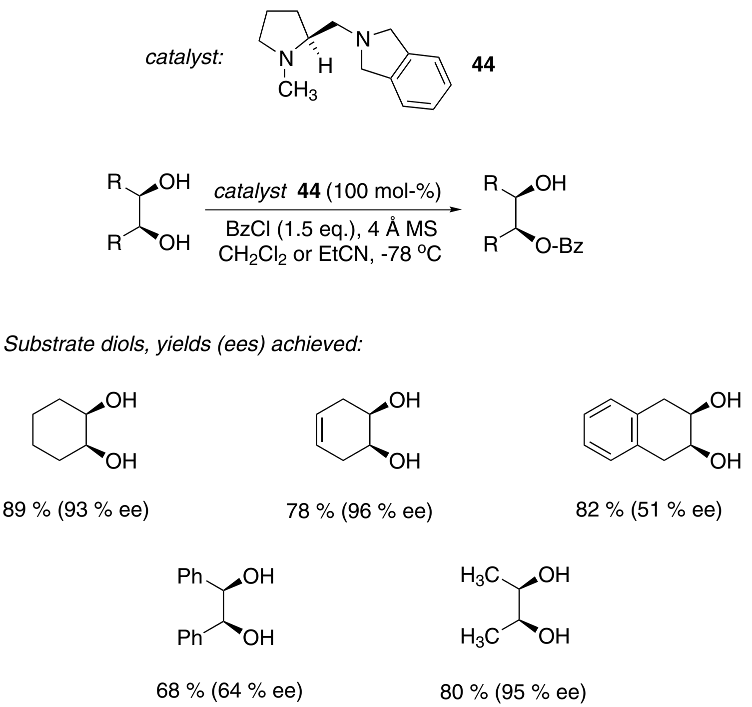
Scheme 13.20



Scheme 13.21

desymmetrized by acylation with benzoyl chloride in the presence of 30 mol% catalyst **39**, with quite satisfactory yields and with enantiomeric excesses of the resulting mono benzoates **41** of up to 93% [35b, c]. These results were obtained with "isolated" catalyst **39**. It should be noted, however, that the phosphinite catalyst **39** can, instead, be generated *in situ* by phosphitylation of cinchonine (**38**) by chlorodiphenylphosphane.

High enantiomeric excess in organocatalytic desymmetrization of *meso*-diols using chiral phosphines as nucleophilic catalysts was achieved for the first time by Vedejs et al. (Scheme 13.21) [36a]. In this approach selectivity factors up to 5.5 were achieved when the C_2-symmetric phospholane **42a** was employed (application of chiral phosphines in the kinetic resolution of racemic secondary alcohols is discussed in Section 12.1). A later study compared the performance of the phospholanes **42b–d** with that of the phosphabicyclooctanes **43a–c** in the desymmetrization of *meso*-hydrobenzoin (Scheme 13.21) [36b]. Improved enantioselectivity was observed for phospholanes **42b–d** (86% for **42c**) but reactions were usually slow. Currently the bicyclic compound **43a** seems to be the best compromise between catalyst accessibility, reactivity, and enantioselectivity – the monobenzoate of hydrobenzoin has been obtained with a yield of 97% and up to 94% ee [36b].

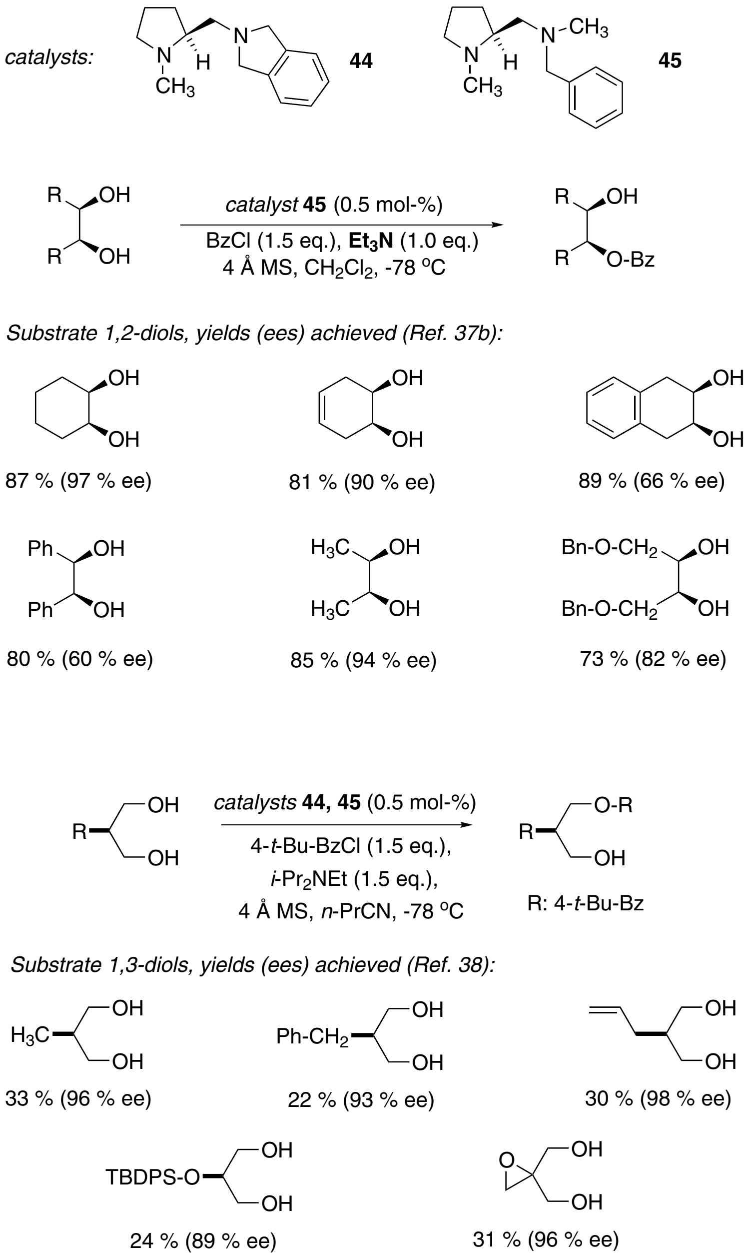


Scheme 13.22

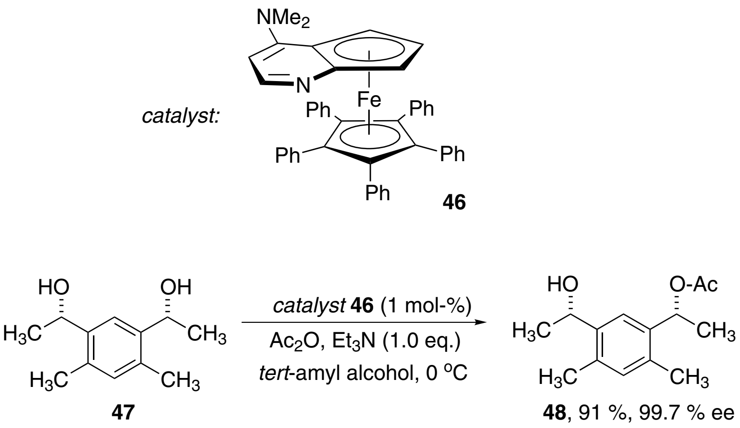
As summarized in Scheme 13.22, Oriyama et al. applied the chiral diamine **44** – albeit in equimolar amounts (relative to the diol) – to the desymmetrization of several *meso*-diols [37a]. In three instances the mono-benzoylated products were obtained with >90% ee and in satisfactory chemical yields [37a].

The same group subsequently discovered that the loading of the chiral diamine catalyst can be reduced substantially if triethylamine is added in stoichiometric amounts as an achiral proton acceptor [37b]. As shown at the top of Scheme 13.23, as little as 0.5 mol% catalyst **45** was sufficient to achieve yields and ee comparable with the stoichiometric variant (application of the Oriyama catalysts **44** and **45** in the kinetic resolution of racemic secondary alcohols is discussed in Section 12.1). Oriyama et al. have also reported that 1,3-diols can efficiently be desymmetrized by use of catalysts **44** or **45**. For best performance *n*-butyronitrile was used as solvent and 4-*tert*-butylbenzoyl chloride as acylating agent (Scheme 13.23, bottom) [38].

Fu et al. used the planar chiral DMAP derivative **46** (Scheme 13.24) [39]. Although this catalyst has been employed successfully for kinetic resolution of a large variety of racemic secondary alcohols (Section 12.1), substrate **47** seems to be the only *meso*-diol that has been desymmetrized by use of the acylation catalyst


catalysts:
44
45
catalyst 45 (0.5 mol-%)
BzCl (1.5 eq.), Et3N (1.0 eq.)
4 Å MS, CH2Cl2, -78 °C
O-Bz
Substrate 1,2-diols, yields (ees) achieved (Ref. 37b):
87 % (97 % ee)
81 % (90 % ee)
89 % (66 % ee)
80 % (60 % ee)
85 % (94 % ee)
73 % (82 % ee)
catalysts 44, 45 (0.5 mol-%)
4-t-Bu-BzCl (1.5 eq.),
i-Pr2NEt (1.5 eq.),
4 Å MS, n-PrCN, -78 °C
R: 4-t-Bu-Bz
Substrate 1,3-diols, yields (ees) achieved (Ref. 38):
33 % (96 % ee)
22 % (93 % ee)
30 % (98 % ee)
24 % (89 % ee)
31 % (96 % ee)

Scheme 13.23



Scheme 13.24

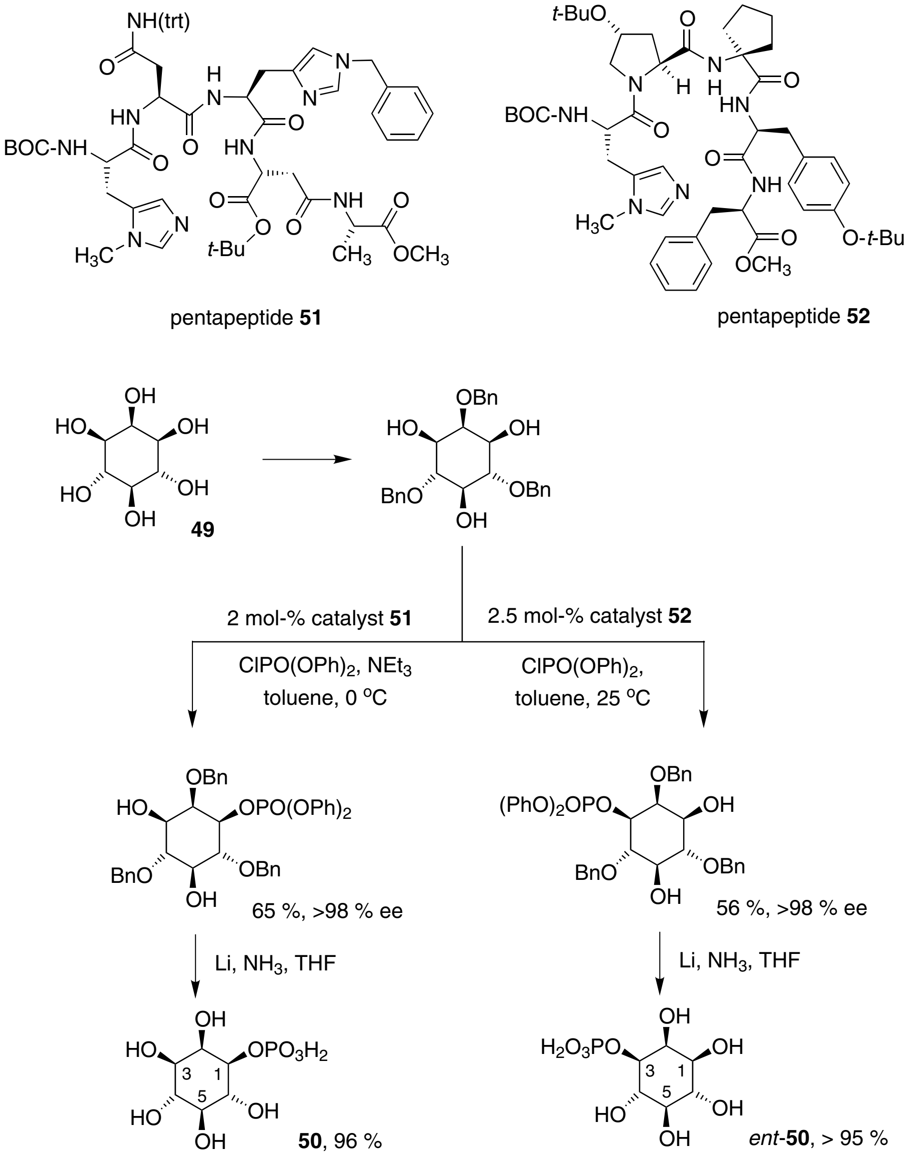
46. As shown in Scheme 13.24, very good enantiomeric excess (99.7%) of the mono-acylation product **48** was achieved [39].

Miller et al. achieved selective functionalization of the enantiotopic hydroxyl groups of *meso*-inositols. In particular, they were able to convert *myo*-inositol **49** to *either* mono-phosphorylated D-*myo*-inositol-1-phosphate **50** *or* D-*myo*-inositol-3-phosphate *ent*-**50** in high yield and with excellent ee (98%) (Scheme 13.25) [40, 41]. This remarkable result was achieved by using the pentapeptides **51** or **52** as catalyst. These catalysts were identified from peptide libraries by a combinatorial approach. The peptides **51** and **52** are highly selective and complementary low-molecular-weight kinase mimics. It is also interesting to note that the opposite enantioselectivity of catalysts **51** and **52** could hardly have been predicted on the basis of the type and sequence of the amino acids involved. (Application of the Miller peptide catalysts to the kinetic resolution of racemic alcohols is discussed in Section 12.1.)

The peptide catalysts **53a–e** incorporating a 4-pyrrolidinopyridine moiety were tested in the desymmetrization of cyclohexane *meso*-1,2- and *meso*-1,3-diols by Kawabata et al. (Scheme 13.26) [42]. As summarized in Scheme 13.26, enantiomeric excesses were up to 65% and chemical yields were in the range 40–77%. (Application of the Kawabata catalysts to the kinetic resolution of racemic alcohols is discussed in Section 12.1.)

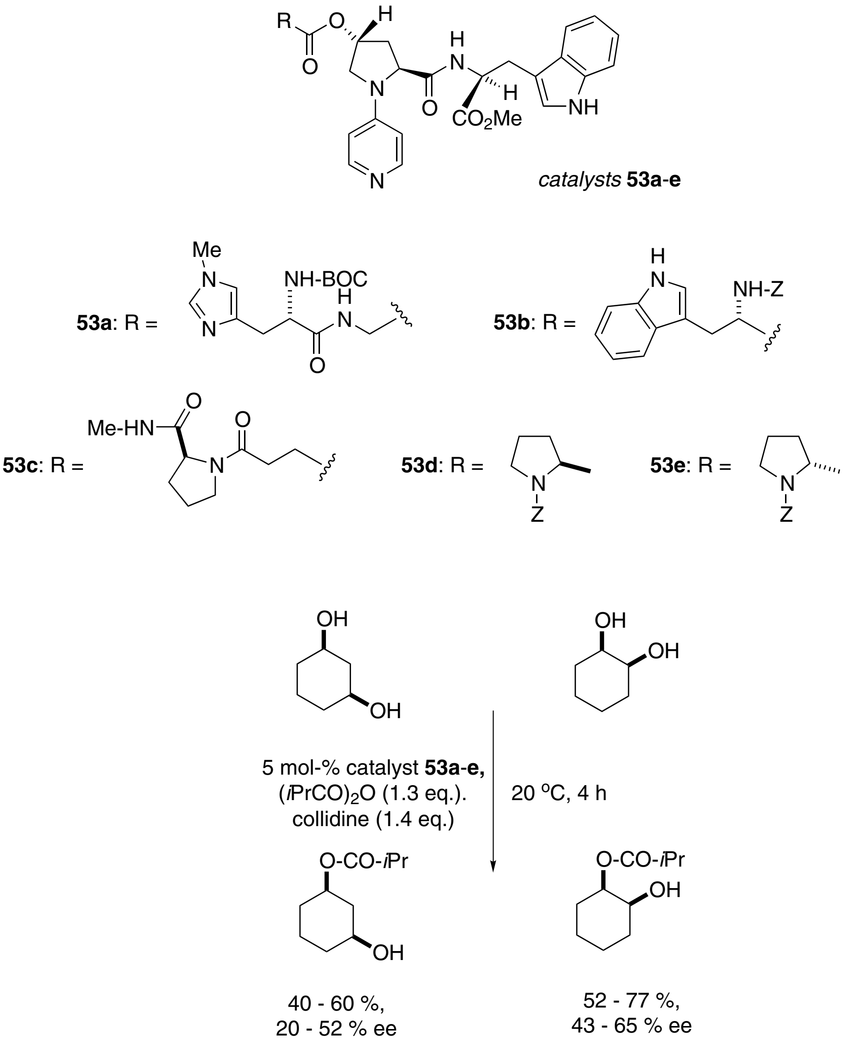
13.3.2
Desymmetrization of *meso*-Diols by Oxidation

Adam et al. subjected a series of *meso*-dihydrobenzoins to oxidative desymmetrization, using three equivalents of the chiral Shi ketone **54** as catalyst. In the presence of peroxomonosulfate (Oxone, Curox etc.), the latter generates a chiral dioxirane as



Scheme 13.25

the active species [43, 44]. As shown in Table 13.1, moderate to good enantiomeric excesses were achieved. In addition to the *meso*-diols, acetonides also proved to be suitable substrates in two instances (Table 13.1). Finally, it should be noted that achiral dioxiranes can be used to generate chiral hydroxyketones from enantiomerically pure diols or acetals [45, 46].



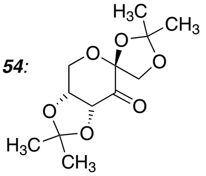
Scheme 13.26

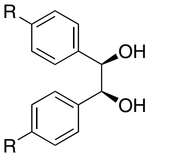
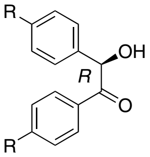
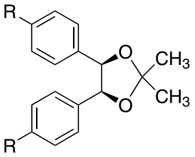
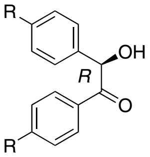
Conclusions

Selectivity in enantiotopos-differentiating acylation and phosphorylation of *meso*-diols can rival that of enzymes. The organocatalysts employed include chiral phosphines, chiral diamines, chiral DMAP derivatives and peptides identified from combinatorial libraries. The highest selectivity in meso diol desymmetrization has been achieved with a planar-chiral Fu catalyst. It seems the substrate scope of this process is not yet broadly explored. Because of their sequential variability it is to be

Tab. 13.1

Shi-ketone ***54***:



Starting meso-diol	*Conversion (%)*		*Product hydroxy ketone*	*ee (%)*
	R = H	89		45
	R = OCH_3	95		24
	R = CH_3	92		30
	R = F	95		58
	R = Cl	56		54
	R = Br	61		58
	R = CN	5		60
	R = H	10		63
	R = CH_3	10		65

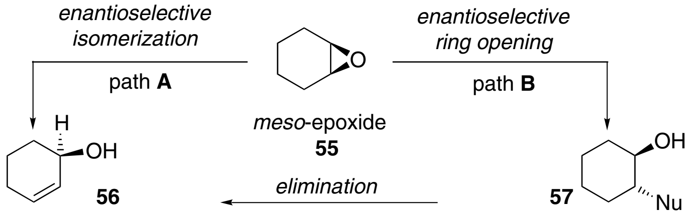
expected that peptide catalysts resulting from combinatorial approaches will afford catalytically active peptides for the efficient desymmetrization of a variety of other diol substrates also. In terms of both yield and selectivity the oxidative desymmetrization of *meso*-diols is not as highly developed as the desymmetrization by acylation.

13.4
Desymmetrization of *meso*-Epoxides

The desymmetrization of *meso*-epoxides such as cyclohexene epoxide (**55**, Scheme 13.27) has been achieved both by enantioselective isomerization, e.g. to allylic alcohols (**56**, path **A**, Scheme 13.27) or by enantiotopos-differentiating opening by nucleophiles, affording trans-β-substituted alcohols and derivatives (**57**, path **B**, Scheme 13.27). As indicated in Scheme 13.27, the allylic alcohols **56** can also be prepared from the ring-opening products **57** by subsequent elimination of the nucleophile.

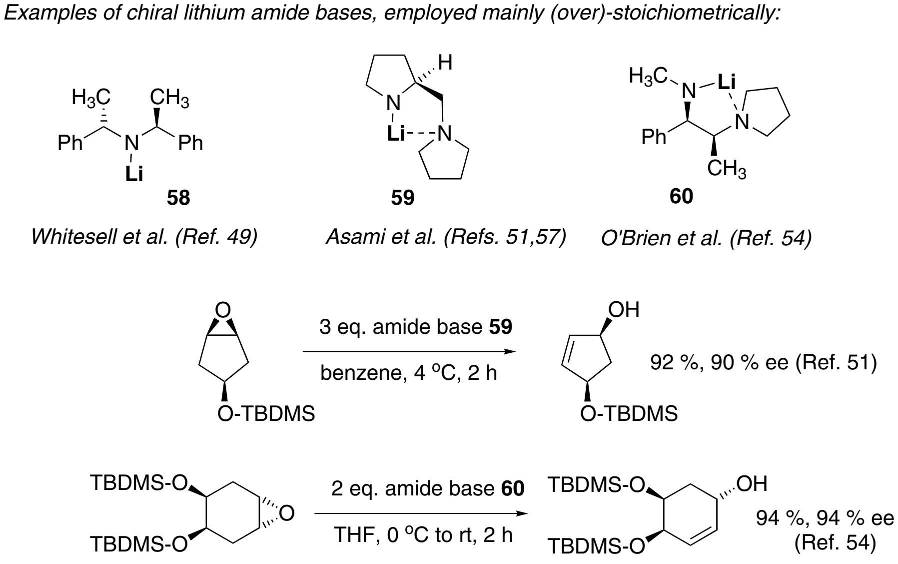
13.4.1
Enantioselective Isomerization of *meso*-Epoxides to Allylic Alcohols

The catalytic isomerization of *meso*-epoxides to allylic alcohols has been achieved with chiral cobalt complexes, in particular with cobalamin (vitamin B_{12}) [47, 48].



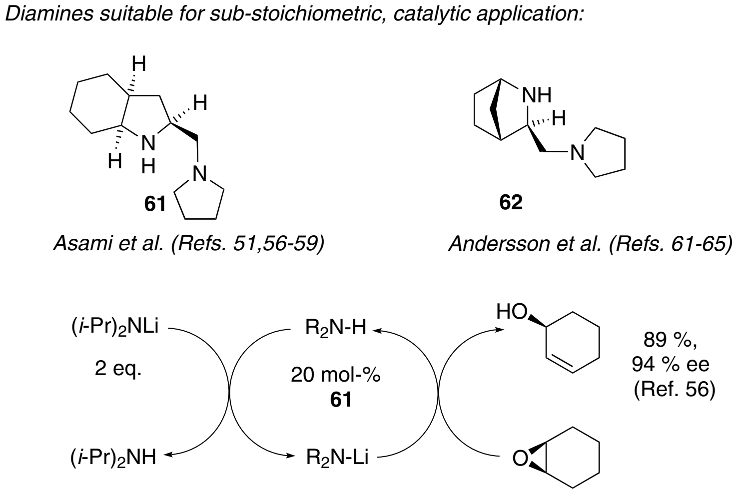
Scheme 13.27

Preparatively more relevant is the use of chiral lithium amide bases, which have been successfully used both for enantioselective generation of allylic alcohols from *meso*-epoxides and for the related kinetic resolution of racemic epoxides [49, 50]. In many instances, chiral amide bases such as **58**, **59**, or **60** were used in stoichiometric or over-stoichiometric quantities, affording synthetically important allylic alcohols in good yields and enantiomeric excesses (Scheme 13.28) [49–54]. Because of the scope of this review, approaches involving stoichiometric use of chiral bases will not be discussed in detail.



Scheme 13.28

Subsequent work [55–65], in particular by Asami [56–60] and Andersson [61–65], has led to the development of *catalytic* methods in which a sub-stoichiometric amount of a chiral diamine such as **61** or **62** is used with an over-stoichiometric quantity of an achiral lithium amide base such as LDA (Scheme 13.29). Examples of catalytic epoxide isomerizations using the Asami diamine **61** or the Andersson



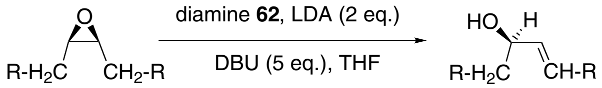
Scheme 13.29

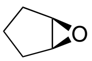
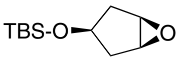
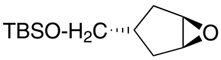
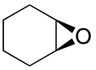
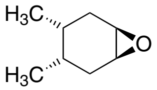
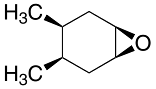
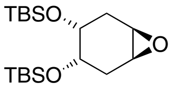
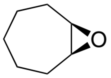
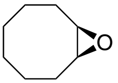
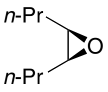
diamine **62** are shown in Schemes 13.29 and 13.30. In particular the diamine **62** has proven very efficient in the catalytic asymmetric isomerization of several epoxides, and enantiomeric excesses > 95% have been achieved for several cyclic substrates (Scheme 13.30) [61, 62].

It should be noted that addition of DBU (or HMPT) has often – particularly for the catalytic procedures – proven beneficial in terms of enantioselectivity. This effect has been attributed to the breaking-up of active but less enantioselective base aggregates [50, 56, 62–64]. Interestingly, when solid-phase-bound stoichiometric (achiral) bases were used instead of LDA, no addition of DBU was necessary [58, 59]. (An example of the stoichiometric use of a chiral solid-phase bound base is given elsewhere [52].) Both experimental and theoretical investigations [66–68] indicate that the base-induced isomerization of epoxides proceeds as a syn elimination, with the lithium ion of the base acting as a Lewis acid (Scheme 13.31).

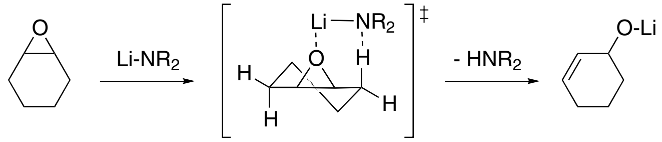
Andersson et al. further improved their diamine catalyst **62** by introduction of substituents on the pyrrolidine ring [63]. Of various catalysts tested, the dimethylated compound **63** proved best (Scheme 13.32) [63]. As summarized in Scheme 13.32, excellent enantiomeric excesses were achieved by use of catalyst loadings as low as 5 mol%, and even for notoriously "difficult" substrates such as cyclopentene epoxide.

As shown in Schemes 13.30 and 13.32, LDA is commonly used as the stoichiometric base, and in the presence of DBU. Recent systematic screening of a variety of lithium amide bases confirmed the superior performance of LDA [64]. It was, however, also found that in the presence of DBU, *n*-BuLi can be used with similar efficiency [64]. Ahlberg et al. have found it is beneficial to replace the commonly used LDA by 2-(lithiomethyl)-1-methylimidazole (**64**, Scheme 13.33) [66]. Under these conditions, 20 mol% of O'Brien's base **60** (Schemes 13.28 and 13.33) afford 93% ee in the isomerization of cyclohexene oxide [66]. Similarly, 2-lithio-1-

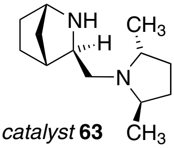


Epoxide	Mol-% **62**	Temp.[°C]	Time [h]	Yield [%]	ee [%]
	20	r.t.	24	67	49
	120	r.t.	24	78	95
	5	0	4	60	67
	120	0	4	85	95
	20	r.t.	48	42	95
	5	0	6	91	96
	5	0	6	95	94
	5	0	16	95	97
	5	0	6	80	97
	5	0	6	89	96
	5	0	36	81	78
	5	0	36	82	66

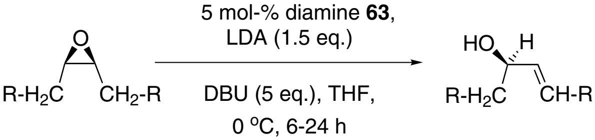
Scheme 13.30

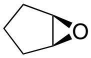
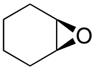
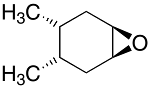
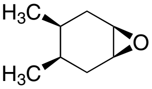
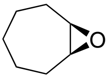
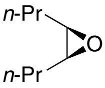


Scheme 13.31

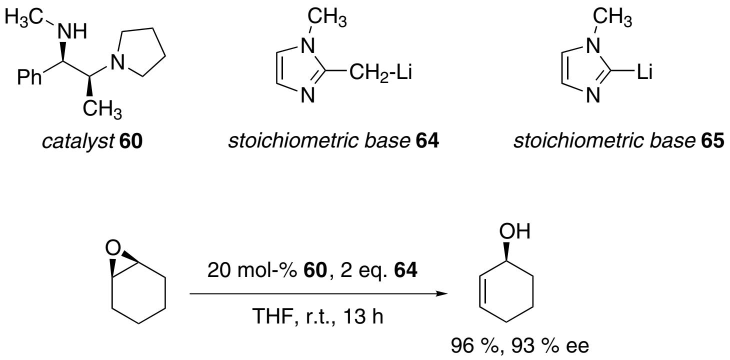


catalyst **63**



Epoxide	Yield [%]	ee [%]
	81	96
	95	99
	94	98
	85	99
	93	>99
	80	91

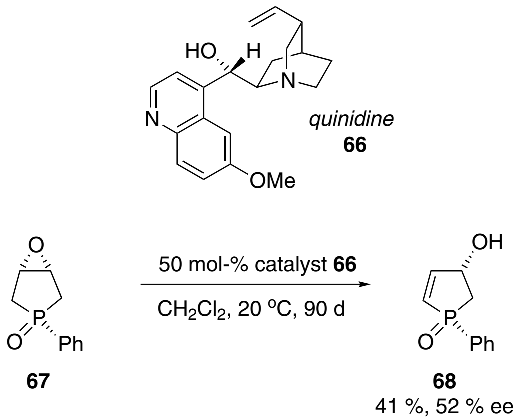
Scheme 13.32



Scheme 13.33

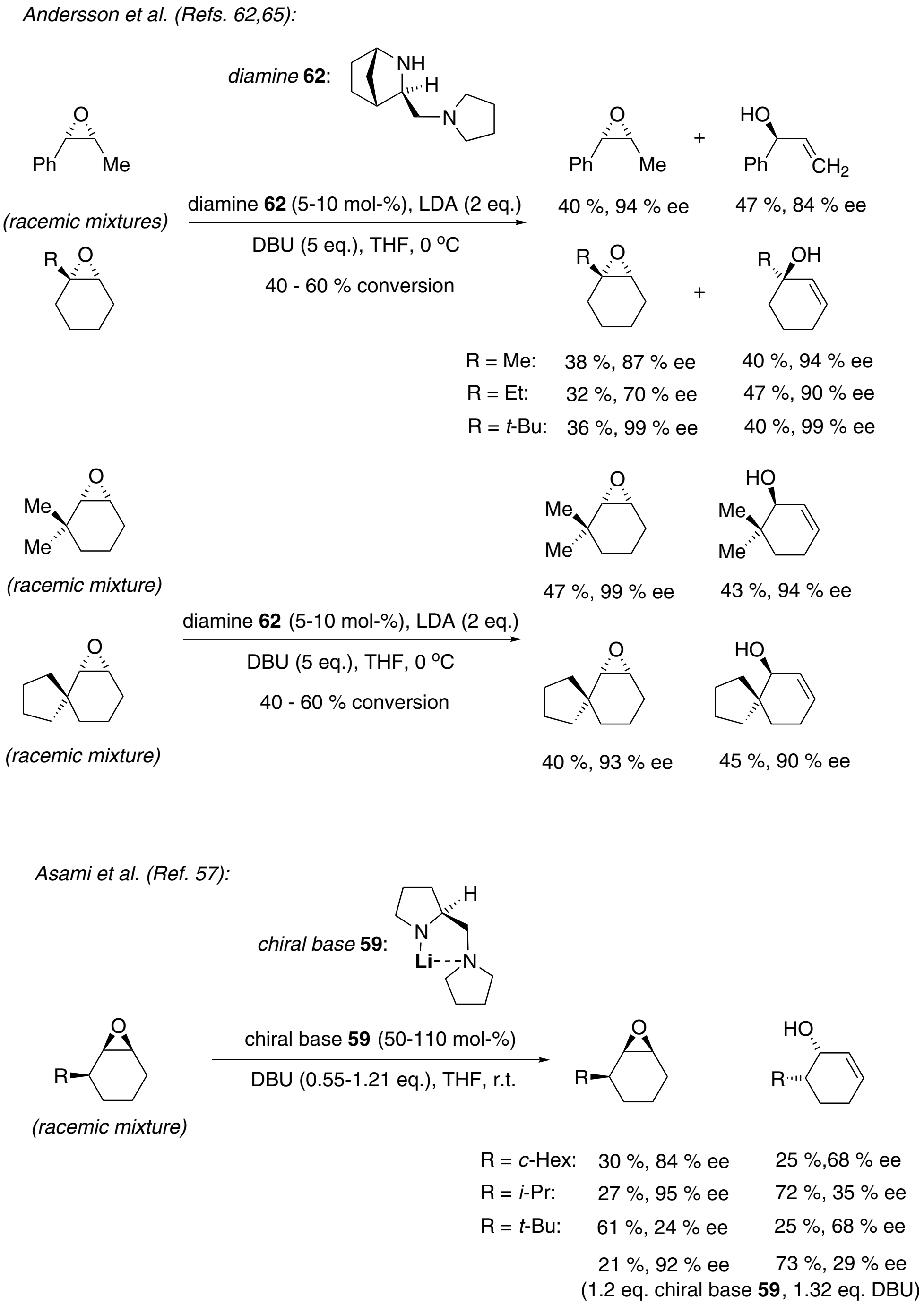
methylimidazole (**65**, Scheme 13.33) was found to perform better as the stoichiometric base than LDA [69]. In combination with the catalytic chiral base **60**, enantiomeric excesses up to 96% were achieved in the isomerization of cyclohexene epoxide [69].

Scheme 13.34 summarizes what seems to be the only "purely" organocatalytic example of base-catalyzed rearrangement of a *meso*-epoxide. In the presence of 50–100 mol% quinidine **66**, the epoxy-3-phospholene **67** was slowly converted to the allylic alcohol **68** with up to 52% ee [70].



Scheme 13.34

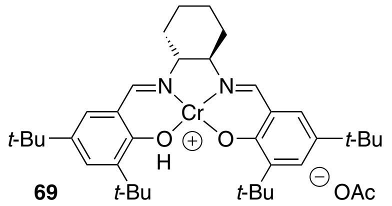
It should finally be mentioned that chiral base methodology is not limited to the desymmetrization of *meso*-epoxides but also enables kinetic resolution of racemic epoxides [57, 63, 65]. This (organocatalytic) type of reaction seems, however, to be less prominent than the desymmetrization of *meso*-epoxides. Some examples of kinetic resolution of chiral epoxides are summarized in Scheme 13.35.

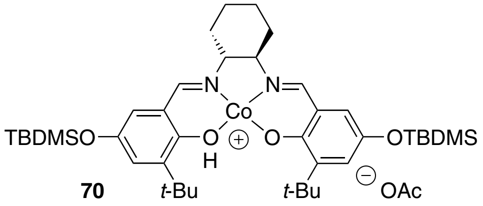

Andersson et al. (Refs. 62,65):
diamine 62:
NH
H
N
O
Ph
Me
(racemic mixtures)
R
O
diamine 62 (5-10 mol-%), LDA (2 eq.)
DBU (5 eq.), THF, 0 °C
40 - 60 % conversion
O
Ph
Me
+
HO
Ph
CH2
40 %, 94 % ee
47 %, 84 % ee
R
O
+
R
OH
R = Me: 38 %, 87 % ee 40 %, 94 % ee
R = Et: 32 %, 70 % ee 47 %, 90 % ee
R = t-Bu: 36 %, 99 % ee 40 %, 99 % ee
O
Me
Me
(racemic mixture)
O
Me
Me
HO
Me
Me
47 %, 99 % ee
43 %, 94 % ee
diamine 62 (5-10 mol-%), LDA (2 eq.)
DBU (5 eq.), THF, 0 °C
40 - 60 % conversion
O
(racemic mixture)
O
HO
40 %, 93 % ee
45 %, 90 % ee
Asami et al. (Ref. 57):
H
chiral base 59:
N
Li
N
O
R
(racemic mixture)
chiral base 59 (50-110 mol-%)
DBU (0.55-1.21 eq.), THF, r.t.
O
R
HO
R
R = c-Hex: 30 %, 84 % ee 25 %,68 % ee
R = i-Pr: 27 %, 95 % ee 72 %, 35 % ee
R = t-Bu: 61 %, 24 % ee 25 %, 68 % ee
21 %, 92 % ee 73 %, 29 % ee
(1.2 eq. chiral base 59, 1.32 eq. DBU)

Scheme 13.35

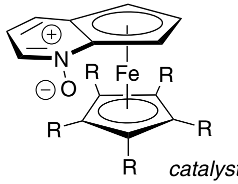
13.4.2
Enantioselective Ring Opening of *meso*-Epoxides

Jacobsen's cobalt and chromium salen complexes **69** and **70** have proven extremely successful in the enantioselective ring opening of *meso*-epoxides (and kinetic resolution of racemic epoxides). Recent accounts of these most efficient and practical catalysts can be found elsewhere [71–73].



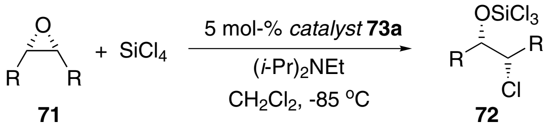


In metal-free catalysis enantioselective ring-opening of epoxides according to Scheme 13.27 path **B** has been achieved both with chiral pyridine *N*-oxides and with chiral phosphoric amides. These compounds act as nucleophilic activators for tetrachlorosilane. In the work by Fu et al. the meso epoxides **71** were converted into the silylated chlorohydrins **72** in the presence of 5 mol% of the planar chiral pyridine *N*-oxides **73** (Scheme 13.36) [74]. As shown in Scheme 13.36, good yields



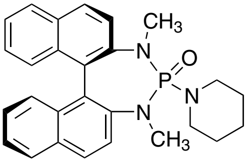
73a: R = 3,5-dimethylphenyl
73b: R = phenyl

catalysts **73**

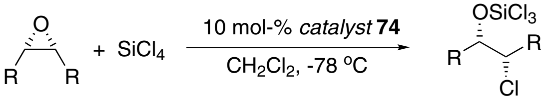


R	Yield [%]	ee [%]
Ph	88	94
4-CH_3-C_4H_4	94	93
4-CF_3-C_4H_4	93	98
4-F-C_4H_4	97	91
2-naphthyl	84	94
CH_2-O-Bn	91	50

Scheme 13.36



catalyst **74**



R	Yield [%]	ee [%]
Ph	94	87
CH_2-O-Bn	95	71
-$(CH_2)_3$-	87	7
-$(CH_2)_4$-	90	52
-$(CH_2)_5$-	95	2

Scheme 13.37

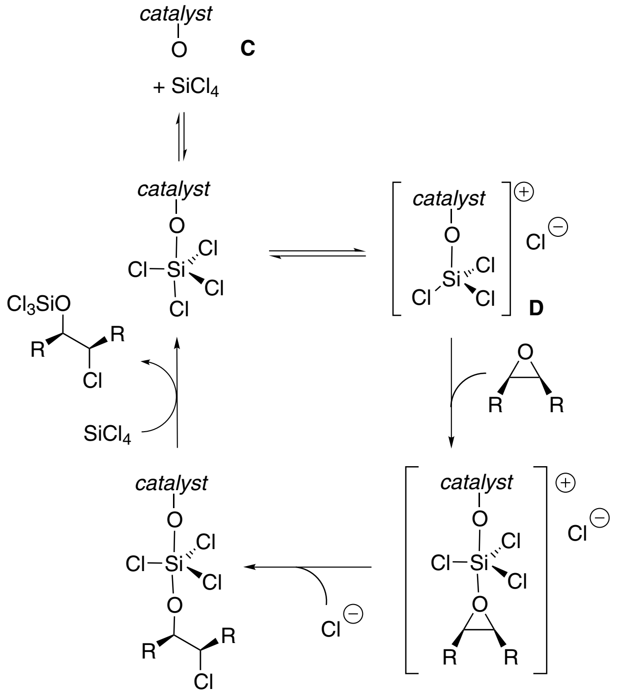
were achieved with catalyst **73a** and enantiomeric excesses > 90% were obtained for *meso* bis-aryl epoxides as substrates. With sterically less demanding catalysts such as **73b** lower enantioselectivity was observed [74].

Denmark et al. employed the chiral phosphoramide **74** (Scheme 13.37) as nucleophilic activator [75]. As summarized in Scheme 13.37, the best enantiomeric excess was observed for *cis*-stilbene oxide (87%). The study revealed that enantioselectivity was highly dependent on the ring size (cyclohexene oxide ≫ cyclopentene oxide > cyclooctene oxide).

With both the Fu and the Denmark catalysts it can be assumed that catalysis is effected by formation of a highly electrophilic silicon cation **D** from tetrachlorosilane and the nucleophilic catalyst **C**, i.e. by attack of the pyridine *N*-oxide or of the phosphoramide *O*-atom on silicon, followed by ionization (Scheme 13.38). The latter cation can then activate the epoxide toward nucleophilic attack by the chloride ion. Exchange of the product silane for another molecule of tetrachlorosilane completes the catalytic cycle [75].

Conclusions

In recent years there has been considerable progress both in the base-catalyzed isomerization of *meso*-epoxides and in the metal-free catalysis of enantioselective opening of meso epoxides. The former approach has proven its potential in sev-



Scheme 13.38

eral synthetic applications, but stoichiometric amounts of (achiral) base are still needed. A chiral catalyst which enables isomerization of a range of different epoxides with high enantioselectivity and with consumption of no other additives remains to be found. The latter method is currently limited to addition of tetrachlorosilane, affording *O*-trichlorosilylated halohydrins. Both chiral pyridine *N*-oxides and phosphoric triamides have been used as catalysts, and enantiomeric excesses $> 90\%$ have been achieved in several instances. It is most probable that catalysis is effected by electrophilic activation of the substrate epoxides by a cationic silane/catalyst complex. It is tempting to speculate whether hydrogen-bonding by designed peptides and peptoids might have similar catalytic effects. The latter approach might enable introduction of nucleophiles other than halides in the course of epoxide opening.

13.5 The Horner–Wadsworth–Emmons Reaction

The enantioselective desymmetrization of prochiral ketones of type **75** by means of the Horner–Wadsworth–Emmons reaction [76, 77] is an elegant means of synthe-

75 76 77

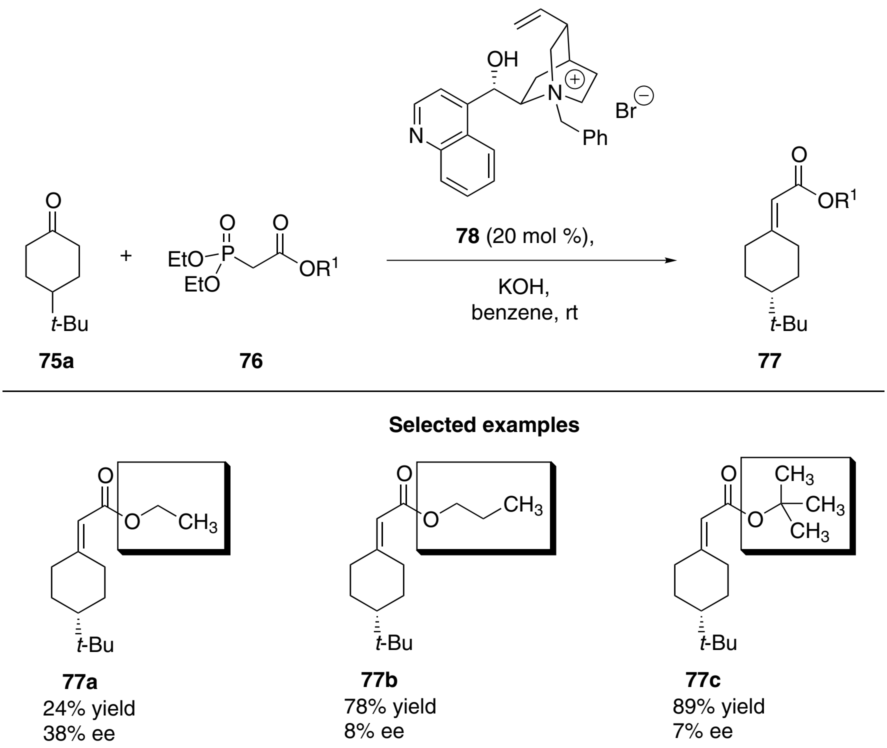
Scheme 13.39

sis of optically active condensation products of type **77**. Those enones with a "remote" stereogenic center are difficult to prepare by other methods. In contrast with many other desymmetrization reactions, which are often based on hydrolytic or oxidative reaction steps, desymmetrization in the Horner–Wadsworth–Emmons reaction is achieved by an olefination process *via* C–C bond-formation. The principle of the asymmetric organocatalytic Horner–Wadsworth–Emmons reaction is shown in Scheme 13.39. To obtain optically active enones, however, stoichiometric amounts of a chiral auxiliary have been required in enantioselective Horner–Wadsworth–Emmons reactions [76, 77].

The first example of a catalytic asymmetric Horner–Wadsworth–Emmons reaction was recently reported by Arai et al. [78]. It is based on the use of a chiral quaternary ammonium salt as a phase-transfer catalyst, **78**, derived from cinchonine. Catalytic amounts (20 mol%) of organocatalyst **78** were initially used in the Horner–Wadsworth–Emmons reaction of ketone **75a** with a variety of phosphonates as a model reaction. The condensation products of type **77** were obtained in widely varying yields (from 15 to 89%) and the enantioselectivity of the product was low to moderate ($\leq$ 43%). Although yields were usually low for methyl and ethyl phosphonates the best enantioselectivity was observed for these substrates (43 and 38% ee, respectively). In contrast higher yields were obtained with phosphonates with sterically more demanding ester groups, e.g. *tert*-butyl, but ee values were much lower. An overview of this reaction and the effect of the ester functionality is given in Scheme 13.40.

In subsequent optimization by the same group improved enantioselectivity of up to 55–57% ee accompanied by satisfactory yields were obtained by use of RbOH instead of KOH as base [78]. In general, *N*-benzyl substituted chinchona derivatives seemed to give the best results.

In conclusion, a catalytic asymmetric Horner–Wadsworth–Emmons reaction using chinchona derivatives as organocatalysts has recently been realized. Because enantioselectivity is currently low to modest, improvement of the reaction to make this route attractive for asymmetric preparation of enantiomerically pure enones of type **77** is certainly a major issue.



Scheme 13.40

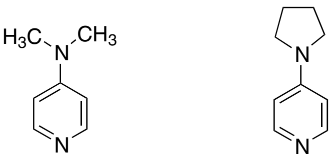
13.6 Rearrangement of *O*-Acyl Azlactones, *O*-Acyl Oxindoles, and *O*-Acyl Benzofuranones

In 1970 Steglich and Höfle reported that 4-dimethylaminopyridine (DMAP) and 4-(pyrrolidino)pyridine (PPY) are excellent catalysts for isomerization of *O*-acyl azlactones **E** to their *C*-acylated isomers **F** [79–81]. In this rearrangement, a new quaternary stereocenter is generated (Scheme 13.41). Clearly, DMAP or PPY afford the rearrangement products **F** in the racemic form.

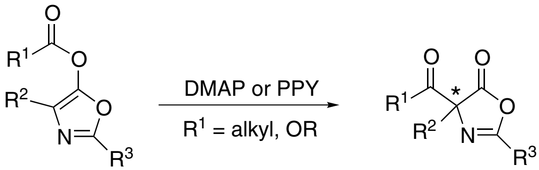
In 1998 Fu and Ruble reported that the planar chiral 4-(diakylamino)pyridine derivatives **79a** and **79b** (Scheme 13.42) induce high enantiomeric excesses in the catalytic *O*-acyl azlactone rearrangement [85, 86]. In particular with the PPY-derivative **79b**, *O*-acyl azlactones **80** were smoothly rearranged to the products **81** in almost quantitative yields and enantiomeric excesses up to 92% (Scheme 13.42) [85].

The rearranged azlactones **81** are versatile starting materials for further transformation, e.g. for reduction to α-substituted serin derivatives such as **82** or for coupling with amino acids, affording, e.g., the dipeptide **83** (Scheme 13.43).

The planar chiral DMAP derivative **79a** proved successful also in the dynamic kinetic resolution of racemic azlactones by ring-opening with alcohols (Scheme



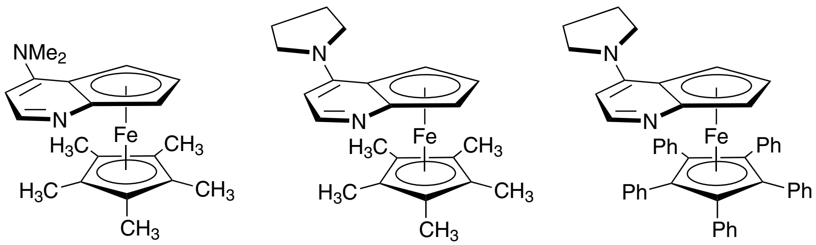
DMAP PPY



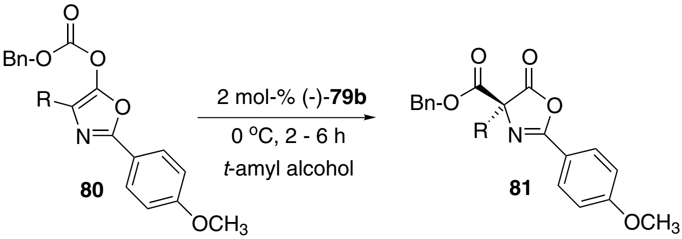
E F

Scheme 13.41

Fu-catalysts **79a-c:**

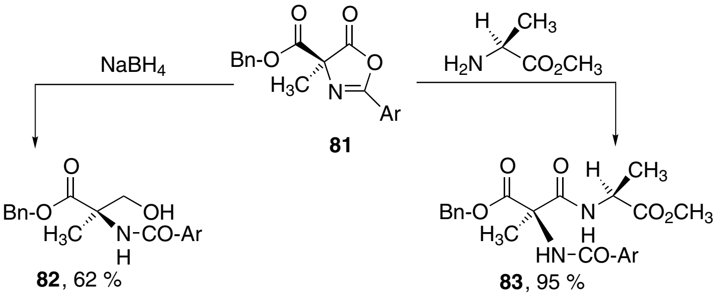


79a **79b** **79c**



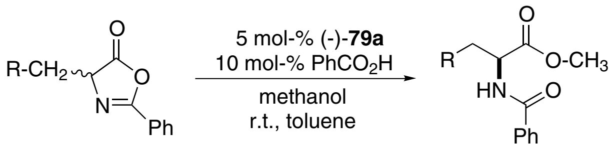
R	Yield [%]	ee [%]
CH_3-	94	91
CH_3-CH_2-	93	90
Ph-CH_2-	93	90
Allyl-	93	91
$(H_3C)_2CH$-CH_2-	95	92
H_3C-S-CH_2-CH_2-	94	88

Scheme 13.42



Scheme 13.43

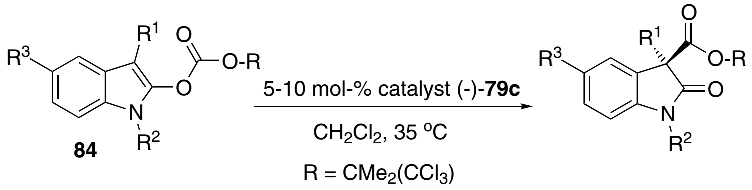
13.44) [87]. This process relies on rapid base-induced racemization of the azlactone and rate-limiting ring opening by the alcohol nucleophile. In this process the DMAP derivative **79a** acts as both Brønsted-basic and as nucleophilic catalyst. With 2-propanol as reagent enantiomeric excesses up to 78% were achieved for the product amino acid esters [87].



R	Yield [%]	ee [%]
H-	98	54
CH_3-	94	44
i-Pr-	95	55
Allyl-	94	61
Cyclohexyl-	93	64
Ph-	94	56
H_3C-S-CH_2-	94	50

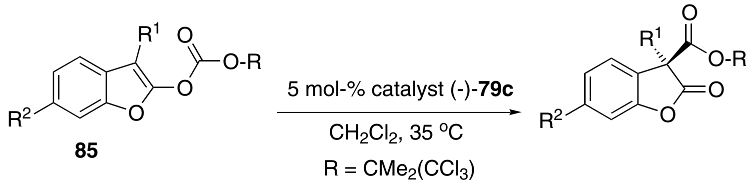
Scheme 13.44

Construction of quaternary stereocenters by enantiocontrolled oxygen to carbon acyl shift is not limited to the azlactone structure. Using the pentaphenylated planar chiral DMAP derivative **79c** (Scheme 13.42) Fu and Hills achieved rearrangement of *O*-acylated oxindoles **84** (Scheme 13.45) and benzofuranones **85** (Scheme 13.46) with very good yields and enantiomeric excesses up to 99% [88].



R^1	R^2	R^3	Yield [%]	ee [%]
Ph	Me	H	91	99
2-Thienyl	Me	H	81	95
Benzyl	Me	H	82	94
Me	Me	H	72	93
Ph	Me	I	94	98
Ph	Bn	H	88	98

Scheme 13.45

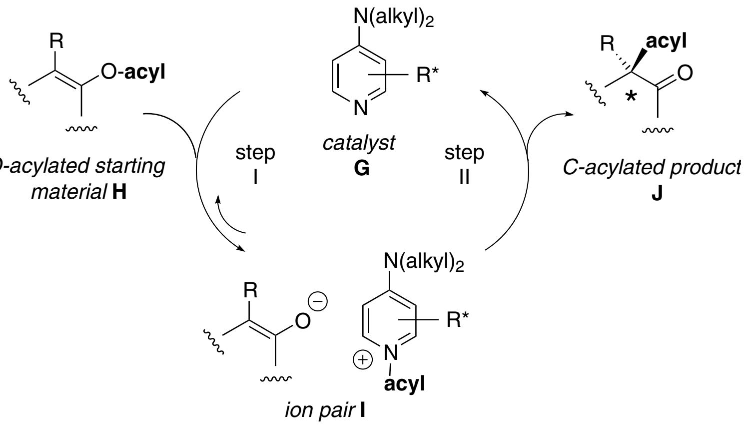


R^1	R^2	Yield [%]	ee [%]
Ph	H	81	97
Benzyl	H	95	88
Me	Me	93	90

Scheme 13.46

The DMAP-catalyzed and thus non-enantioselective version of the latter rearrangement was reported in 1986 by Black et al. [89, 90].

All three isomerizations discussed above seem to occur by analogous mechanistic pathways similar to the mechanism formulated for the Dakin–West reaction [82]. Deacylation of the starting material **H** by catalyst **G** affords, in a fast and reversible step (Scheme 13.47, step I), an acylpyridinium/enolate ion-pair **I**. From this ion pair, enantioselective C-acylation proceeds in the rate-determining and irreversible second step, furnishing the C-acylated product **J** (Scheme 13.47, step II).



Scheme 13.47

Conclusion

This chapter summarizes three related and highly effective approaches to the catalytic asymmetric generation of quaternary stereocenters – organocatalytic rearrangements of *O*-acyl azlactones to their C-acylated isomers and analogous isomerizations of *O*-acyl oxindoles and *O*-acyl benzofuranones. All three processes hold great promise for application in, e.g., natural product synthesis [91–93].

References

1 For a recent summary of developments in the metal-based and metal-free catalytic desymmetrization of meso anhydrides with alcohols, see: A. P. Spivey, B. I. Andrews, *Angew. Chem.* **2001**, *113*, 3227–3230; *Angew. Chem. Int. Ed.* **2001**, *40*, 3131–3134.

2 (a) For a recent review on the organocatalytic asymmetric alcoholysis of cyclic anhydrides, see: Y. Chen, P. McDaid, L. Deng, *Chem. Rev.* **2003**, *103*, 2965–2983; (b) For a general review on enantioselective desymmetrization, see: M. C. Willis, *J. Chem. Soc., Perkin Trans. 1*, **1999**, 1765–1784.

3 (a) H. B. Kagan, J. C. Fiaud, *Topics Stereochem.* **1988**, *18*, 249–330; (b) K. Faber, *Chem. Eur. J.* **2001**, *7*, 5005–5010; (c) J. Eames, *Angew. Chem.* **2000**, *112*, 913–916; *Angew. Chem. Int. Ed.* **2000**, *39*, 885–888.

4 J. Hiratake, Y. Yamamoto, J.-I. Oda, *J. Chem. Soc., Chem. Commun.* **1985**, 1717–1719.

5 J. Hiratake, M. Inagaki, Y. Yamamoto, J.-I. Oda, *J. Chem. Soc., Perkin Trans. 1* **1987**, 1053–1058.

6 M. Inagaki, J. Hiratake, Y. Yamamoto, J.-I. Oda, *Bull. Chem. Soc. Jpn.* **1987**, *60*, 4121–4126.

7 R. A. Aitken, J. Gopal, J. A. Hirst, *J. Chem. Soc., Chem. Commun.* **1988**, 632–634.

8 R. A. Aitken, J. Gopal, *Tetrahedron: Asymmetry* **1990**, *1*, 517–520.

9 C. Bolm, A. Gerlach, C. L. Dinter, *Synlett* **1999**, 195–196.

10 C. Bolm, I. Schiffers, C. L. Dinter,

A. Gerlach, *J. Org. Chem.* **2000**, *65*, 6984–6991.
11 C. Bolm, I. Schiffers, I. Atodiresei, C. P. R. Hackenberger, *Tetrahedron: Asymmetry* **2003**, *14*, 3455–3467.
12 C. P. R. Hackenberger, I. Schiffers, J. Runsink, C. Bolm, *J. Org. Chem.* **2004**, *69*, 739–743.
13 C. Bolm, I. Schiffers, C. L. Dinter, L. Defrère, A. Gerlach, G. Raabe, *Synthesis* **2001**, 1719–1730.
14 J. Mittendorf, J. Benet-Buchholz, P. Fey, K.-H. Mohrs, *Synthesis* **2003**, 136–140.
15 Y. Chen, S.-K. Tian, L. Deng, *J. Am. Chem. Soc.* **2000**, *122*, 9542–9543.
16 C. Choi, S.-K. Tian, L. Deng, *Synthesis* **2001**, 1737–1741.
17 Y. Uozomi, K. Yasoshima, T. Miyachi, S. Nagai, *Tetrahedron Lett.* **2001**, *42*, 411–414.
18 M. Ostendorf, R. Romagnoli, I. C. Pereiro, E. C. Roos, M. J. Moolenaar, W. N. Speckamp, H. Hiemstra, *Tetrahedron: Asymmetry* **1997**, *8*, 1773–1789.
19 L. Tang, L. Deng, *J. Am. Chem. Soc.* **2002**, *124*, 2870–2871.
20 J. Hang, S.-K. Tian, L. Tang, L. Deng, *J. Am. Chem. Soc.* **2001**, *123*, 12696–12697.
21 J. Hang, H. Li, L. Deng, *Org. Lett.* **2002**, *4*, 3321–3324.
22 J. Hang, L. Deng, *Synlett* **2003**, 1927–1930.
23 Y. Chen, L. Deng, *J. Am. Chem. Soc.* **2001**, *123*, 11302–11303.
24 (a) C. Mazzini, J. Lebreton, V. Alphand, R. Furstoss, *Tetrahedron Lett.* **1997**, *38*, 1195–1198; (b) A. Schoenfelder, A. Mann, S. Coz, *Synlett* **1993**, 63–64.
25 H. Kunz, H. Waldmann, *Angew. Chem.* **1984**, *96*, 49–50; *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 71–72.
26 H. Pracejus, *Justus Liebigs Ann. Chem.* **1960**, *634*, 9–22.
27 H. Pracejus, G. Kohl, *Justus Liebigs Ann. Chem.* **1969**, *722*, 1–11.
28 (a) H. Pracejus, A. Tille, *Chem. Ber.* **1963**, *96*, 854–865; (b) H. Pracejus, H. Mätje, *J. Prakt. Chem.* **1964**, *24*, 195–205.
29 For the use of polymer-bound cinchona alkaloids in this type of reaction, see: T. Yamashita, H. Yasveda, Y. Miyavchi, N. Nakamura, *Bull. Chem. Soc. Jpn.* **1977**, *50*, 1532–1534.
30 B. L. Hodous, J. C. Ruble, G. C. Fu, *J. Am. Chem. Soc.* **1999**, *121*, 2637–2638.
31 Because the ferrocene moiety of **3** and **4** fulfills a purely structural role and does not participate directly in the catalysis, the nucleophilic catalysts **3** and **4** are considered "metal-free" and are thus included in this account.
32 H. Pracejus, *Justus Liebigs Ann. Chem.* **1960**, *634*, 23–29.
33 S. Winter, H. Pracejus, *Chem. Ber*, **1966**, *99*, 151–159.
34 B. L. Hodous, G. C. Fu, *J. Am. Chem. Soc.* **2002**, *124*, 10006–10007.
35 (a) L. Duhamel, T. Herman, *Tetrahedron Lett.* **1985**, *26*, 3099–3102; (b) S. Mizuta, M. Sadamori, T. Fujimoto, I. Yamamoto, *Angew. Chem.* **2003**, *115*, 3505–3507; *Angew. Chem. Int. Ed.* **2003**, *42*, 3383–3385; (c) In the desymmetrization of *meso*-hydrobenzoin, 92% ee was also achieved with 10 mol% of the catalyst **39**.
36 (a) E. Vedejs, O. Daugulis, S. T. Diver, *J. Org. Chem.* **1996**, *61*, 430–431; (b) E. Vedejs, O. Daugulis, N. Tuttle, *J. Org. Chem.* **2004**, *69*, 1389–1392.
37 (a) T. Oriyama, K. Imai, T. Hosoya, T. Sano, *Tetrahedron Lett.* **1998**, *39*, 397–400; (b) T. Oriyama, K. Imai, T. Sano, T. Hosoya, *Tetrahedron Lett.* **1998**, *39*, 3529–3532.
38 T. Oriyama, H. Taguchi, D. Terakado, T. Sano, *Chem. Lett.* **2002**, 26–27.
39 J. C. Ruble, J. Twedell, G. C. Fu, *J. Org. Chem.* **1998**, *63*, 2794–2795.
40 B. R. Sculimbrene, S. J. Miller, *J. Am. Chem. Soc.* **2001**, *123*, 10125–10126.
41 B. R. Sculimbrene, A. J. Morgan, S. J. Miller, *J. Am. Chem. Soc.* **2002**, *124*, 11653–11656.
42 T. Kawabata, R. Stragies, T. Fukaya, Y. Nagaoka, H. Schedel, K. Fuji, *Tetrahedron Lett.* **2003**, *44*, 1545–1548.

43 W. Adam, C. R. Saha-Möller, C.-G. Zhao, *Tetrahedron: Asymmetry* **1998**, *9*, 4117–4122.
44 W. Adam, C. R. Saha-Möller, C.-G. Zhao, *J. Org. Chem.* **1999**, *64*, 7492–7497.
45 L. D'Accolti, A. Detomaso, C. Fusco, A. Rosa, R. Curci, *J. Org. Chem.* **1993**, *58*, 3600–3601.
46 R. Curci, L. D'Accolti, A. Dinoi, C. Fusco, A. Rosa, *Tetrahedron Lett.* **1996**, *37*, 115–118.
47 R. Scheffold, H. Su, L. Walder, Z.-da Zang, *Helv. Chim. Acta* **1988**, *71*, 1073–1078.
48 P. Bonhote, R. Scheffold, *Helv. Chim. Acta* **1991**, *74*, 1425–1444.
49 First report on the isomerization of meso epoxides with chiral Li-amide bases: J. K. Whitesell, S. W. Felman, *J. Org. Chem.* **1980**, *45*, 755–756.
50 For recent reviews, see: (a) A. Magnus, S. K. Bertilsson, P. G. Andersson, *Chem. Soc. Rev.* **2002**, *31*, 223–229; (b) J. Eames, *Eur. J. Org. Chem.* **2002**, 393–401.
51 (a) M. Asami, S. Inoue, *Tetrahedron* **1995**, *51*, 11725–11730; (b) M. Asami, M. Ogawa, S. Inoue, *Tetrahedron Lett.* **1999**, *40*, 1563–1564.
52 For solid-phase-attached lithiated 1-phenylethylamine, providing significantly higher ee than 1-phenylethylamine itself, see: A. Johansson, P. Abrahamsson, Ö. Davidsson, *Tetrahedron: Asymmetry* **2003**, *14*, 1261–1266.
53 P. C. Brookes, D. J. Milne, P. J. Murphy, B. Spolaore, *Tetrahedron* **2002**, *58*, 4675–4680.
54 S. E. de Sousa, P. O'Brien, C. D. Pilgram, *Tetrahedron* **2002**, *58*, 4643–4654.
55 J. P. Tierney, A. Alexakis, P. Mangeney, *Tetrahedron: Asymmetry* **1997**, *8*, 1019–1022.
56 M. Asami, T. Suga, K. Honda, S. Inoue, *Tetrahedron Lett.* **1997**, *38*, 6425–6428.
57 M. Asami, S. Sato, K. Honda, S. Inoue, *Heterocycles* **2000**, *52*, 1029–1032.
58 M. Asami, A. Seki, *Chem. Lett.* **2002**, 160–161.
59 A. Seki, M. Asami, *Tetrahedron* **2002**, *58*, 4655–4663.
60 T. Yoshida, K. Sakakibara, M. Asami, *Chem. Lett.* **2003**, 150–151.
61 M. J. Södergren, P. G. Andersson, *J. Am. Chem. Soc.* **1998**, *120*, 10760–10761.
62 M. J. Södergren, S. K. Bertilsson, P. G. Andersson, *J. Am. Chem. Soc.* **2000**, *122*, 6610–6618.
63 S. K. Bertilsson, M. K. Södergren, P. G. Andersson, *J. Org. Chem.* **2002**, *67*, 1567–1573.
64 S. K. Bertilsson, P. G. Andersson, *Tetrahedron* **2002**, *58*, 4665–4668.
65 A. Gayet, S. Bertilsson, P. G. Andersson, *Org. Lett.* **2002**, *4*, 3777–3779.
66 S. O. N. Lill, D. Pettersen, M. Amedjkouh, P. Ahlberg, *J. Chem. Soc., Perkin Trans. 1* **2001**, 3054–3063.
67 D. Pettersen, M. Amedjkouh, S. O. N. Lill, K. Dahlén, P. Ahlberg, *J. Chem. Soc., Perkin Trans. 2* **2001**, 1654–1661.
68 T. Yoshida, K. Sakakibara, M. Asami, *Chem. Lett.* **2003**, *32*, 150–151.
69 M. Amedjkouh, D. Petterson, S. O. N. Lill, Ö. Davidsson, P. Ahlberg, *Chem. Eur. J.* **2001**, *7*, 4368–4377.
70 K. M. Pietrusiewicz, M. Koprowski, Z. Pakulski, *Tetrahedron: Asymmetry* **2002**, *13*, 1017–1019.
71 E. N. Jacobsen, M. H. Wu in *Comprehensive Asymmetric Catalysis* (E. N. Jacobsen, A. Pfaltz, H. Yamamoto, eds.), Springer, Heidelberg, **1999**, 1309–1326.
72 E. N. Jacobsen, *Acc. Chem. Res.* **2000**, *33*, 421–431.
73 J. M. Ready, E. N. Jacobsen, *Angew. Chem.* **2002**. *114*, 1432–1435; *Angew. Chem. Int. Ed. Engl.* **2002**, *41*, 1374–1377.
74 B. Tao, M. M.-C. Lo, G. C. Fu, *J. Am. Chem. Soc.* **2001**, *123*, 353–354.
75 S. E. Denmark, P. A. Barsanti, K.-T. Wong, R. A. Stavenger, *J. Org. Chem.* **1998**, *63*, 2428–2429.
76 For reviews about the asymmetric Horner–Wadsworth–Emmons reaction, see: (a) T. Rein, L. Vares, T. M. Pedersen, P.-O. Norrby,

P. Brandt, D. Tanner, *Phosphorus, Sulfur, Silicon Related Elem.* **1999**, *144–146*, 169–172; (b) J. Motoyoshiya, *Trends Org. Chem.* **1998**, *7*, 63–73; (c) M. Yamaguchi, M. Hirama, *Chemtracts: Org. Chem.* **1994**, *7*, 401–405.

77 For selected asymmetric Horner–Wadsworth–Emmons reactions using stoichiometric amount of a chiral auxiliary, see: (a) B. M. Trost, D. P. Curran, *J. Am. Chem. Soc.* **1980**, *102*, 5699–5700; (b) S. Hanessian, S. Beaudoin, *Tetrahedron Lett.* **1992**, *33*, 7659–7662; (c) N. Kann, T. Rein, *J. Org. Chem.* **1993**, *58*, 3802–3804; (d) M. S. Van Nieuwenhze, K. B. Sharpless, *J. Am. Chem. Soc.* **1993**, *115*, 9864–7865; (e) N. Komatsu, S. Matsunaga, T. Sugita, S. Umemura, *J. Am. Chem. Soc.* **1993**, *115*, 5847–5848; (f) S. E. Denmark, I. Rivera, *J. Org. Chem.* **1994**, *59*, 6887–6889; (g) T. Kumamoto, K. Koga, *Chem. Pharm. Bull.* **1997**, *45*, 753–755, and references cited therein.

78 S. Arai, S. Hamaguchi, T. Shioiri, *Tetrahedron Lett.* **1998**, *39*, 2997–3000.

79 W. Steglich, G. Höfle, *Tetrahedron Lett.* **1970**, 4727–4730.

80 For a recent optimized derivative of the DMAP catalyst, see: M. R. Heinrich, H. S. Klisa, H. Mayr, W. Steglich, H. Zipse, *Angew. Chem.* **2003**, *115*, 4975–4977; *Angew. Chem. Int. Ed.* **2003**, *42*, 4826–4828.

81 For reviews on the chemistry of 4-(dialkylamino)pyridines, see Refs. [82–84].

82 G. Höfle, W. Steglich, H. Vorbrüggen, *Angew. Chem.* **1978**, *90*, 602–615; *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 569–583.

83 A. Hassner, L. R. Krepski, V. Alexanian, *Tetrahedron* **1978**, *34*, 2069–2076.

84 E. F. V. Scriven, *Chem. Soc. Rev.* **1983**, *12*, 129–161.

85 J. C. Ruble, G. C. Fu, *J. Am. Chem. Soc.* **1998**, *120*, 11532–11533.

86 G. C. Fu, *Acc. Chem. Res.* **2000**, *33*, 412–420.

87 J. Liang, J. C. Ruble, G. C. Fu, *J. Org. Chem.* **1998**, *63*, 3154–3155.

88 I. D. Hills, G. C. Fu, *Angew. Chem.* **2003**, *115*, 4051–4054; *Angew. Chem. Int. Ed.* **2003**, *42*, 3921–3924.

89 T. H. Black, S. M. Arrivo, J. S. Schumm, J. M. Knobeloch, *J. Chem. Soc., Chem. Commun.* **1986**, 1524–1525.

90 T. H. Black, S. M. Arrivo, J. S. Schumm, J. M. Knobeloch, *J. Org. Chem.* **1987**, *52*, 5425–5430.

91 For an auxiliary-controlled, diastereoselective example of the *Black* rearrangement, aiming at the synthesis of diazonamide A, see Ref. [92].

92 E. Vedejs, J. Wang, *Org. Lett.* **2000**, *2*, 1031–1032.

93 See footnote 15 in Ref. [88] for the use of the *Black* rearrangement in the formal total synthesis of debromoaplysin.

14
Large-scale Applications of Organocatalysis

14.1
Introduction

The potential of a catalytic process for use on a large scale can be a good indication of its efficiency. During recent decades there has been an increasing tendency to apply asymmetric catalytic processes in industry [1]. The asymmetric Noyori hydrogenation [2] and the Sharpless and Jacobsen–Katsuki epoxidation [3] are representative examples of impressive developments in this field [1].

Seeking new and innovative technology platforms, the chemical industry is also showing increasing interest in organocatalytic reactions as a potential solution for large-scale applications. For example, the increased tendency to use organocatalysis as a tool for commercial applications in addition to biocatalysis [4] and metal-catalysis [1] is emphasized by the increasing number of patent applications describing the synthesis of organocatalysts and their use in synthetic applications [5].

Organocatalysis has several advantages not only in respect of its synthetic range but also for economic reasons. Thus, one might expect that in the future an increasing number of organocatalytic reactions will make the jump from academic synthesis to industrial application. The beneficial impact of organocatalytic reactions on large-scale production of chiral building blocks has already been demonstrated, even though the number of examples is still limited. Selected case studies of larger-scale applications will be discussed in section 14.3.

14.2
Organocatalysis for Large-scale Applications: Some General Aspects and Considerations

What are the key advantages for industrial chemists focusing on an organocatalytic reaction as a (potential) solution for a large-scale process? In the following text these issues will be discussed and an attempt will be made to describe "general advantages and drawbacks". Because organocatalysis is, however, a broad field covering a high diversity of catalysts and reactions, the authors are aware that a general answer for organocatalysis as a whole is not possible, and that there are many positive or negative exceptions.

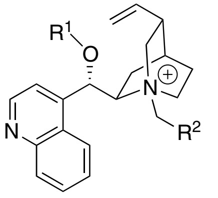
Asymmetric Organocatalysis. Albrecht Berkessel and Harald Gröger
Copyright © 2005 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim
ISBN: 3-527-30517-3

Among the main criteria which must be discussed when assessing an organocatalytic reaction as a potential solution for a large-scale process [6] are:

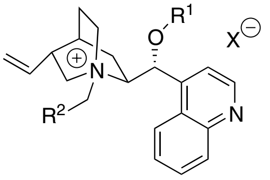
- economy of the catalyst (price/availability)
- stability of the catalysts, and handling issues
- recycling issues: immobilization of organocatalysts
- enantioselectivity, conversion, and catalyst loading

14.2.1 Economy of the Catalyst (Price/Availability)

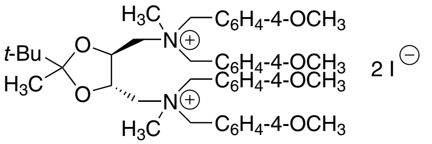
Certainly in this category one can see a major advantage of organocatalysis. Many organocatalysts are readily available and inexpensive raw materials from the "chiral pool" or are simple derivatives thereof. Representative examples of the many organocatalysts of economic interest are alkaloids and derivatives thereof (e.g. types **1** and **2**), tartaric acid (for preparation of the Shibasaki catalyst **3**), L-proline **4**, and natural amino acids, which function, e.g., as starting materials for MacMillan catalysts of type **5**. An overview of these representative economically attractive organocatalysts is given in Scheme 14.1. The economically attractive price of these



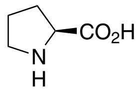
1



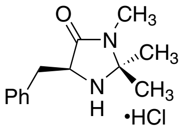
2



3



4



5

Scheme 14.1

catalysts might also "justify" the higher catalytic loadings occasionally required, in particular proline catalysis with catalytic amounts typically in the range of 20–35 mol% (although here it has already been reported that reactions can also be conducted with much lower catalyst loadings).

14.2.2
Stability of the Catalysts and Handling Issues

Another advantage of organocatalysts is their stability and handling. For most organocatalysts there are no concerns with regard to moisture sensitivity, which can be a serious issue for chiral metal complexes used as Lewis acid catalysts. Thus, special equipment for handling organocatalysts is often not required. Taking L-proline, amino acid-based catalysts (e.g. the MacMillan catalysts for numerous reactions [7] and the poly-L-Leu catalyst for epoxidation [8]), and alkaloid catalysts as representative examples, these compounds are stable and work well in the presence of water. Selected examples are alkaloid-based chiral phase-transfer catalysts in aqueous/organic two-phase solvent systems used for asymmetric alkylation and Michael addition processes (see also Chapters 3 and 4, for example) and the asymmetric Mannich reaction in the presence of L-proline as organocatalyst, which tolerates up to 10% (*v*/*v*) water (Ref. [9] and Section 5.2).

14.2.3
Recycling Issues: Immobilization of Organocatalysts

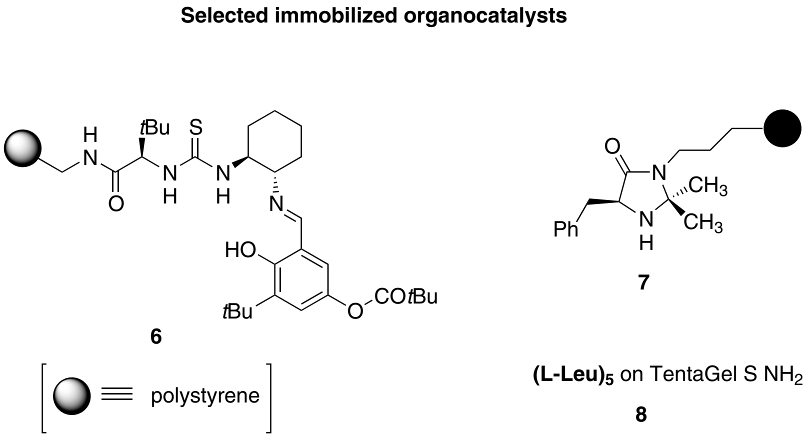
The possibility of recycling a catalyst has an important impact on catalyst costs, in particular for catalysts which must be prepared in multi-step syntheses, which require the use of expensive starting materials, or which are needed in large quantities.

Recovery of organocatalysts for re-use after downstream-processing has already been reported for some processes (see also the discussion below on immobilization). For example, recovery and re-use has been investigated for L-proline catalysis [10].

Immobilization is a popular means of simplifying separation of a catalyst from the reaction mixture. In contrast with immobilized metal complexes (via a solid-support-bound ligand) leaching problems are a less critical issue when using organocatalysts immobilized by covalent bonding to the solid support.

Several organocatalysts have been recycled efficiently (selected examples are shown in Scheme 14.2). For example, the Jacobsen group has reported results from an impressive study of the recycling of the immobilized urea derivative **6**, a highly efficient organocatalyst for asymmetric hydrocyanation of imines (Scheme 14.2) [11]. It was discovered that the catalyst can be recycled and re-used very efficiently – over ten reaction cycles the product was obtained with similar yield and enantioselectivity (96–98% yield, 92–93% ee).

In addition, immobilized catalysts related to the MacMillan imidazolidinone-type organocatalyst **5** have been used for the asymmetric Diels–Alder reaction (Section



Scheme 14.2

8.1) [12a]. In particular the solid-supported imidazolidinone **7** was found to be a very efficient immobilized organocatalyst. It should be noted that solid-supported catalysts of type **7** usually gave results equal or superior to those obtained with the analogous "free" solution-phase catalyst. Recovery and re-use of the solid-supported catalysts **7** have led to similar results.

Immobilized proline has also been tested but, in contrast, gave less satisfactory results than L-proline itself [12b]. L-Proline is, however, an inexpensive catalyst which can be recycled efficiently without immobilization [10] and was also found to be suitable in catalytic amounts below 10 mol% [13b]. There might, therefore, be less need for immobilization of L-proline than for other, more expensive, catalysts.

An example of catalysts which are themselves heterogeneous are the poly-amino acids used for the asymmetric Juliá–Colonna-type epoxidation of chalcones using alkaline hydrogen peroxide (Section 10.2) [8]. Because of the highly efficient synthesis of epoxides, this process also has attracted industrial interest (Section 14.3). Since recent work by the Berkessel group revealed that as few as five L-Leu residues are sufficient for epoxidation of chalcone, several solid-phase-bound short-chain peptides have been used, leading to enantioselectivity up to 98% ee [14]. For example, (L-Leu)$_5$ immobilized on "TentaGel S NH_2", **8**, was found to be a suitable solid-supported short-chain peptide catalyst for epoxidations.

Several other organocatalysts have also been immobilized (these applications are described in the appropriate chapters of this book). Thus, immobilization of organocatalysts has already been achieved successfully and found to be a suitable tool for simple catalyst recovery and re-use.

14.2.4 Enantioselectivity, Conversion, and Catalytic Loading

Despite impressive results, the enantioselectivity obtained does not often exceed 98% ee. Because enantiomeric purity of > 99% ee is required for pharmaceutical purposes, subsequent work-up and refining steps must be added to improve enan-

tioselectivity. To avoid such subsequent purification, further fine tuning of many catalysts is desirable. Besides asymmetric induction, conversion and productivity are also important.

Thus, high conversion, possibly after a short reaction time, is required, as is low catalytic loading. With regard to the last issue, optimization of many organocatalytic reactions is certainly still needed. Typical amounts of catalyst are in the range 10–20 mol%. For L-proline amounts of catalyst in the range of 20–35 mol% are used frequently [13]. Although L-proline is a cheap catalyst, reduction of catalyst loading is, nevertheless, of interest. Representative studies for the aldol and Mannich reactions have already shown that the reaction works with lower catalyst loadings [13b].

Although the combination of high conversion, good yield, high enantioselectivity (and diastereoselectivity if there are more than one stereogenic center) at low (organo-)catalytic loadings of, e.g., 1 mol% or below is still a challenge for many reactions, examples of such efficient systems are already available. In particular these types of reaction are already of much interest for large-scale applications.

Among many excellent organocatalytic syntheses from numerous groups in which excellent enantioselectivity of ≥99% ee is combined with high yields at low catalytic loadings of ≤5–20 mol% (occasionally only 1 mol% or below), some selected highlights are summarized below.

In the field of asymmetric organocatalytic *alkylation* (see also Section 3.1) impressive examples with enantioselectivity ≥ 99% ee have been reported by the Corey group, the Park and Jew group, and the Maruoka group [15–17]. Different types of catalyst have been used, with amounts of catalyst in the range 0.2 to 10 mol%. High enantioselectivity (99%) has also been achieved for asymmetric *halogenation* reactions (see also Section 3.4). This has been demonstrated for chlorination and bromination reactions by Lectka and co-workers [18].

Asymmetric *nucleophilic addition to C=C double bonds* (see also Chapter 4) can also proceed highly stereoselectively. Several examples of enantio- and diastereoselective *Michael additions* with 99% ee for the resulting products have been described by the Corey group [19]. A cinchonidine-derived phase-transfer organocatalyst (10 mol%) was used.

In the field of asymmetric *nucleophilic additions to C=N double bonds* (see also Chapter 5), *hydrocyanations of imines* which proceed with >99% ee have been reported by the Lipton [20] and Jacobsen [21] groups. Diketopiperazines (2 mol%) and urea-type organocatalysts (1 mol%), respectively, were used. The List and Barbas groups found that enantioselective *Mannich reactions* can proceed with ≥99% ee when using L-proline (5–20 mol%) as organocatalyst [22, 23]. The Lectka group developed a highly enantio- and diastereoselective *ketene-addition to imines* [24]. Optically active β-lactams with ≥99% ee have been obtained by use of 5–10 mol% cinchona alkaloid-type organocatalysts.

Highly enantioselective syntheses have also been reported for *additions to C=O double bonds* (see also Chapter 6). Examples of L-proline-catalyzed *intermolecular aldol-reactions* furnishing aldol adducts bearing one and two stereogenic centers with >99% ee have been reported by List and co-workers [25]. The same group also described a highly diastereo- and enantioselective organocatalytic *intramolecular aldol reaction* which proceeds with 99% ee [26]. Asymmetric organocatalytic *Baylis–*

Hillman reactions leading to products with 99% ee have been reported by the Hatakeyama group [27]. The reaction was performed with 10 mol% of an alkaloid-type organocatalyst.

The Jørgensen group demonstrated that nucleophilic *addition to N=N double bonds* (see also Section 7.1) can proceed with >99% ee [28]. L-Proline was used as catalyst for the α-amination reaction. L-Proline-catalyzed *additions to N=O double bonds* (see also Section 7.2) furnishing products with 99% ee have been developed by the MacMillan group, the Zhong group, the Hayashi group and the Cordova group [29–31].

The MacMillan group has also shown that *cycloaddition reactions* (see also Chapter 8) can be performed highly diastereo- and enantioselectively. The [3+2]-cycloaddition of nitrones and α,β-unsaturated carbonyl compounds in the presence of 20 mol% of a phenylalanine-derived imidazolidinone acid salt led to products with 99% ee [32]. An example of an enantioselective *rearrangement reaction* (see also Section 13.6) with 99% ee has been reported by the Fu group [33], who used 2 mol% of a planar chiral DMAP derivative as catalyst.

In conclusion, these selected examples emphasize that highly efficient organocatalysts are already available for a broad range of organic transformations and enable the synthesis of the desired target molecules with enantioselectivity ≥ 99% ee. Many other examples which give high enantioselectivity (e.g. >95% ee) and enable further, subsequent enantiomeric enrichment are also known. Thus, for many organocatalytic transformations the enantioselectivity, conversion, yield, and amount of catalyst are already in the range which makes them attractive for large-scale syntheses.

14.3 Large-scale Organocatalytic Reaction Processes (Selected Case Studies)

This section reports selected case studies of organocatalytic reactions which have already been scaled up or which are process technology solutions with the potential for scale-up. These examples emphasize the potential of organocatalytic reactions for commercial-scale applications. The scale-up of the corresponding reactions ranges from larger lab scale applications to applications on a technical scale. The case studies discussed are:

- Case Study 1: Juliá–Colonna-type epoxidation
- Case Study 2: Hydrocyanation of imines
- Case Study 3: Alkylation of cyclic ketones and glycinates
- Case Study 4: The Hajos–Parrish–Eder–Sauer–Wiechert reaction

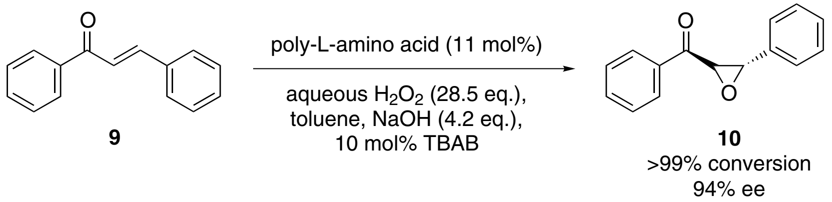
14.3.1 Case Study 1: Juliá–Colonna-type Epoxidation

In 1980 Julia et al. reported a simple asymmetric epoxidation catalyzed by polyamino acids [8, 34]. Subsequently, many groups have contributed to the further

development of this synthetic method, which has been found to be an efficient technique for preparation of chalcone-type epoxides (see also Section 10.2). The epoxidation reaction uses hydrogen peroxide as oxidant and proceeds under three-phase conditions. Among the main advantages of this epoxidation reaction are the use of an environmentally friendly organocatalyst and relatively cheap oxidant and base (NaOH), the potential recyclability of the organocatalyst, and the high enantioselectivity – up to ≥95% ee. For commercial application, however, this method also has some drawbacks [35]. For example, large excesses of catalyst – amounts up to 200% (*w*/*w*) – are needed. The catalyst must also be preactivated, a process which takes more than 6 h. Another drawback is a long reaction time – from 1 to 5 days – which significantly limits commercial applicability.

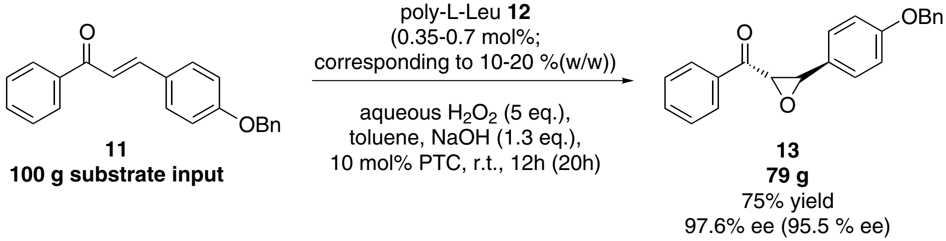
Researchers at Bayer AG addressed these critical issues and developed successful solutions enabling commercial application of Julia–Colonna-type epoxidation [35–40]. Starting with optimization of catalyst preparation, a straightforward synthesis based on inexpensive reagents and requiring a shorter reaction time was developed for the poly-Leu-catalyst [35]. In particular, the reaction time for the new polymerization process was only 3 h when the process was conducted at 80 °C in toluene, compared with 5 days under classic reaction conditions (THF, room temperature). Furthermore, the catalyst prepared by the "Bayer route" is much more active and does not require preactivation [35–40].

In parallel, the three-phase reaction system was improved. It was found that the reaction was strongly enhanced when performed in the presence of a phase-transfer catalyst as achiral additive [35–40]. Epoxidation of chalcone **9** with 10 mol% TBAB led to >99% conversion within 7 min and high enantioselectivity of 94% ee (Scheme 14.3) [35]. In the absence of TBAB the asymmetric poly-L-leucine-catalyzed epoxidation afforded only 2% conversion after 1.5 h. It was also reported that the amount of catalyst could be further reduced.



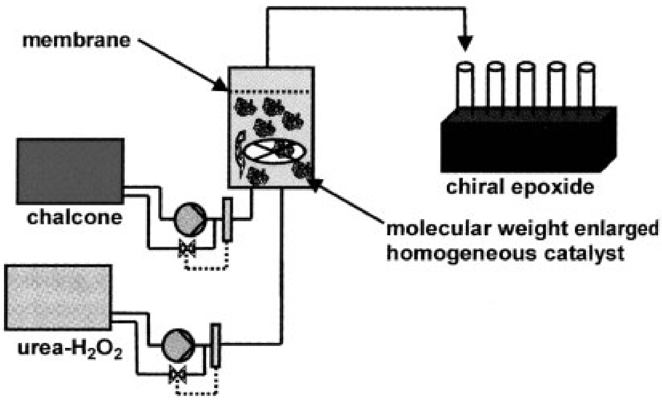
Scheme 14.3. PTC catalyst.

A first scale-up to the 100 g scale was recently reported (Scheme 14.4) [35]. Use of a catalytic amount (10–20%, *w*/*w*) of the poly-L-Leu organocatalyst **12**, equivalent to 0.35–0.7 mol%, led to complete conversion and 75% yield of **13** after isolation. The enantioselectivity of the product **13** was 97.6% ee. On this larger, 100 g-scale, however, a prolonged reaction time of 12 h was required, rather than the 7 min for the small-scale reaction. It was also found that efficient stirring was essential for complete conversion. It should be noted that the catalyst can be re-used without loss of reactivity and enantioselectivity [35].



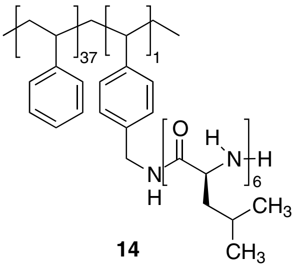
Scheme 14.4

Researchers at Degussa AG focused on an alternative means towards commercial application of the Juliá–Colonna epoxidation [41]. Successful development was based on design of a continuous process in a chemzyme membrane reactor (CMR reactor). In this the epoxide and unconverted chalcone and oxidation reagent pass through the membrane whereas the polymer-enlarged organocatalyst is retained in the reactor by means of a nanofiltration membrane. The equipment used for this type of continuous epoxidation reaction is shown in Scheme 14.5 [41]. The chemzyme membrane reactor is based on the same continuous process concept as the efficient enzyme membrane reactor, which is already used for enzymatic α-amino acid resolution on an industrial scale at a production level of hundreds of tons per year [42].



Scheme 14.5. CMR reactor (From Ref. [41] with permission of the Georg-Thieme-Verlag).

The prerequisite for this process, namely the availability of homogenous polymer-supported catalysts, was fulfilled by Tsogoeva et al. who developed, for example, the oligo(L-Leu) catalyst **14** (Scheme 14.6) [41]. This catalyst has been used efficiently in the continuous CMR process with chalcone and urea–hydrogen peroxide as oxidizing agent. The epoxidation reaction in a 10-mL chemzyme membrane reactor, catalyzed by **14**, furnished the epoxide product with enantioselectivity up to 90–95% throughout 50 residence times [41]. In conclusion, the advan-



14

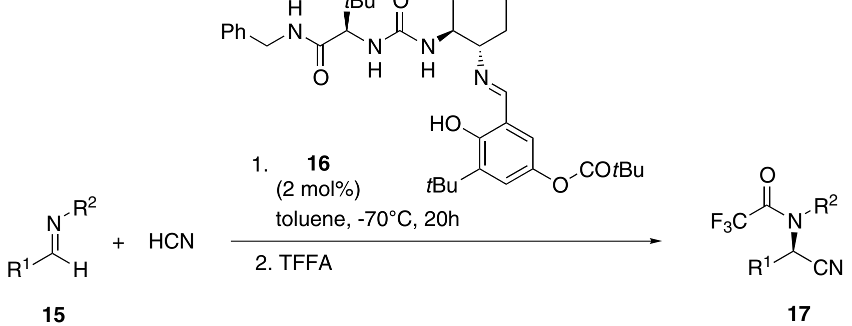
Scheme 14.6

tages of this CMR concept with soluble polymer-supported oligo(L-Leu) are efficient conversion in combination with both high catalyst activity and enantioselectivity [41].

It should be mentioned here that in addition to the Juliá–Colonna epoxidation, the Shi epoxidation is also attracting commercial interest. In a recent presentation DSM reported current activity on the application of the Shi technology on a commercial scale [43].

14.3.2
Case Study 2: Hydrocyanation of Imines

The asymmetric catalytic Strecker reaction is an elegant means of synthesis of optically active α-amino acids. The Jacobsen group developed optimized organocatalysts [21, 44–48], optically active urea or thiourea derivatives, which were found to be the most efficient type of catalyst yet for asymmetric hydrocyanation of imines (see also Section 5.1 on the hydrocyanation of imines). Because of its high efficiency, Jacobsen hydrocyanation technology has already been used commercially at Rodia ChiRex [49]. The concept of the reaction is shown in Scheme 14.7. In the presence of a catalytic amount (2 mol%) of the readily available organocatalyst

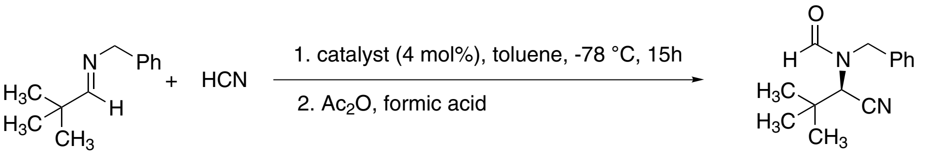


15 17

Scheme 14.7. Rhodia ChiREx concept.

16 the asymmetric hydrocyanation proceeds with high conversion and enantioselectivity for a broad range of imines. The resulting α-amino nitrile products are conveniently isolated as the trifluoracetamides **17**, which can be further converted into a range of enantiomerically pure building blocks, e.g. α-amino acids [49].

In addition, minor variation of the catalyst in combination with immobilization on a resin support gave an analogous recyclable solid-supported organocatalyst. Varying the derivatization method by trapping the α-amino nitrile intermediate with formic acid and acetic anhydride gives the crystalline formamides **19** in excellent yield and with high enantioselectivity. These features of this catalytic process have been demonstrated by results from the synthesis of L-*tert*-leucine (Scheme 14.8) [49].



18

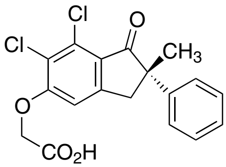
19
10 cycles of the catalyst
97-98% yield per cycle
92-93% ee per cycle

Scheme 14.8

Rhodia ChiRex have reported that this organocatalytic Jacobsen-type Strecker reaction is now being exploited commercially and delivers highly enantiomerically enriched natural and unnatural α-amino carboxylic acids quickly, smoothly, and in bulk [49].

14.3.3
Case Study 3: Alkylation of Cyclic Ketones and Glycinates

In the mid-1980s Merck chemists developed a method for asymmetric alkylation of a cyclic ketone in the presence of a simple cinchona alkaloid (see also Section 3.1) [50–52]. The resulting product **23**, bearing a quaternary stereogenic center, is an intermediate in the synthesis of indacrinone **20** (Scheme 14.9). It should be noted that this impressive contribution from Merck chemists was not only the first exam-

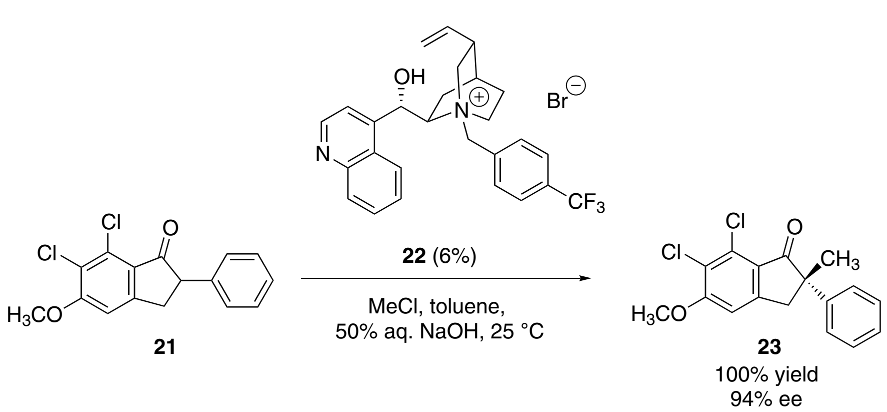


20

Scheme 14.9

ple of a highly asymmetric PTC-catalyzed alkylation but also one of the first asymmetric organocatalytic syntheses applied on a large scale.

Starting with enantioselectivity below 10% ee, increased asymmetric induction was achieved by using individually made cinchona-derived quaternary ammonium salts. Whereas use of *N*-benzylcinchoninium enabled ca. 30% ee to be achieved, use of analogous *p*-substituted derivatives gave enantioselectivity up to 60% ee. Subsequent process development led to an efficient enantioselective alkylation process with enantioselectivity up to 94% ee (Scheme 14.10) [50–52]. The yield of the desired product was 100% and the amount of catalyst required was 6% only. This process was also was found to be suitable for scaling up. The large-scale feasibility of this process was demonstrated successfully on a pilot-plant scale [50]. By means of this methodology, drug supply by this program was realized, until the demise of the candidate for reasons of toxicity [50].



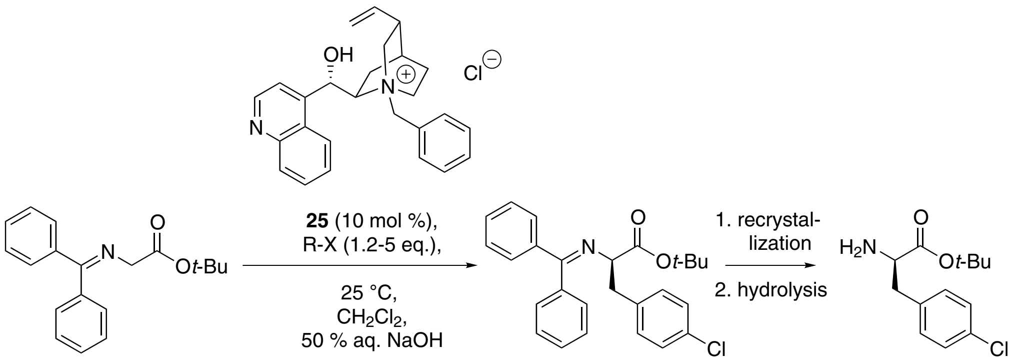
Scheme 14.10

The power of this phase-transfer method is also emphasized by the economics of the process. It was reported that the cost of producing the desired (*S*) enantiomer on the basis of the asymmetric organocatalytic alkylation route using an amount of catalyst below 10 mol% was significantly lower than the cost of producing the isomer by a resolution process [50].

In conclusion, this synthesis of the indacrinone intermediate **23** developed by Merck researchers is a highly efficient and technically feasible method for asymmetric alkylation. It not only afforded the desired drug intermediate **23** in quantitative yield and high enantioselectivity but was also found to be suitable for technical applications, as has been demonstrated on a pilot-plant scale.

Further great advances in the field of asymmetric alkylation reactions have been made by several groups working on chiral phase-transfer-catalyzed alkylation of glycinates (see also Section 3.1). A pioneer in this field is the O'Donnell group [53, 54] who developed the first α-amino acid ester synthesis using this methodol-

ogy. It should be noted that they also reported the first scale up of the synthesis in a multi-gram-scale preparation of the α-amino acid D-*p*-chlorophenylalanine [54]. The asymmetric alkaloid-catalyzed alkylation with a *p*-chlorobenzyl halide proceeds with formation of the glycinate in 81% yield and with 66% ee when using 10 mol% catalyst (Scheme 14.11). Subsequent recrystallization and then hydrolysis afforded 6.5 g of an enantiomerically pure sample of the "free" amino acid D-*p*-chlorophenylalanine [54].



24
multi gram scale synthesis

26
81% yield
66% ee

27
enantiomerically pure D-phenylalanine: 6.5 g

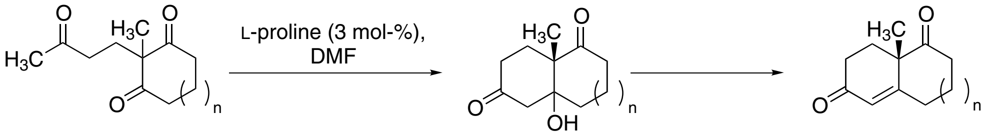
Scheme 14.11

In addition to the work of the O'Donnell group, further important contributions in the field of asymmetric alkylation have been made by the groups of Lygo, Corey, Maruoka, Shiori, Kim, and Jew and Park (see also Section 3.2). The last group [55–59] also used their alkaloid-based PTC-catalyst in a 150-gram-scale application for synthesis of a *p*-substituted phenylalanine derivative [60]. It should be noted that results similar to those from the small-scale (50-mg) process have been obtained by conducting the reactions on a 150-gram scale, thus indicating the potential feasibility of this reaction for scale up and applications on a larger scale. Several patent applications also describe the use of alkaloid-type glycinate alkylation technology for preparation of target molecules of commercial interest [5a, 55, 59, 61].

Despite the great achievements made over the years in alkaloid-type asymmetric alkylation of glycinates, however, to the best of our knowledge commercial application of this method on an industrial scale for production of optically active α-amino acids has not yet been reported. Nevertheless, because of the high efficiency achieved by use of the "state of the art" of this methodology, the prerequisite for applications on industrial scale have now been realized, and commercial applications can be expected in the future.

14.3.4
Case Study 4: The Hajos–Parrish–Eder–Wiechert–Sauer Reaction

The Hajos–Parrish–Eder–Wiechert–Sauer reaction, developed independently by two industrial groups in the early nineteen-seventies, was one of the first major contributions of organocatalysis (see also Section 6.2.2 on the asymmetric intramolecular aldol reaction) [62–66]. The target molecules **32** and **33** are valuable intermediates in the asymmetric synthesis of steroids, and were envisaged as alternatives to rare natural sources as means of access to these compounds [13b]. Both groups used L-proline as organocatalyst. At Hoffmann LaRoche, Hajos and Parrish showed that triketones **28** and **29** give, in an intramolecular aldol reaction, the aldol products **30** and **31**, which can subsequently be transformed into the desired target products **32** and **33** [62–64]. In the presence of only 3 mol% L-proline the intramolecular aldol reaction proceeds with enantioselectivity of 74–96% ee (Scheme 14.12).



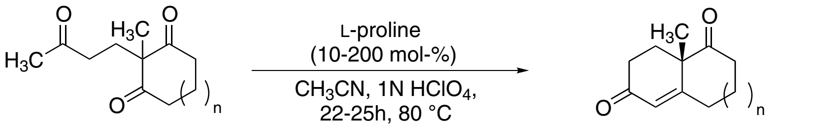
28: n=0
29: n=1

30: n=0, 100% yield, 93% ee
31: n=1, 52% yield, 74% ee

32: n=0
33: n=1

Scheme 14.12

Schering chemists demonstrated that the target molecules **32** and **33** can also be synthesized in a one-pot reaction with enantioselectivity up to 84% ee when using 10–200 mol% proline as catalyst [65, 66]. Because of easy access to the steroid precursors **28** and **29** from readily available raw materials, and the use of the economically attractive catalyst L-proline, this intramolecular aldol reaction has attracted commercial attention. At Schering L-proline catalysis has been conducted on a multi-kilogram scale [67].



28: n=0
29: n=1

32: n=0, 86.8% yield, 84% ee
33: n=1, 83% yield, 71% ee

Scheme 14.13

Conclusion

In conclusion, the process development and scale up already achieved for several organocatalytic reactions have shown that organocatalysis can be a valuable tool

for industrial-scale solutions. It can also be expected that the broad variety of efficient organocatalytic syntheses already developed, in combination with further breakthroughs and new applications, will contribute to an increasing number of organocatalytic large-scale reactions in the future.

References

1 H. U. Blaser, E. Schmidt (Eds), *Asymmetric Catalysis on Industrial Scale*, Wiley–VCH, Weinheim, **2004**.

2 For a review, see: R. Noyori, *Angew. Chem. Int. Ed. Engl.* **2002**, *41*, 2008–2022.

3 For reviews, see: (a) T. Katsuki in: *Comprehensive Asymmetric Catalysis I–III* (Eds: E. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, **1999**, pp. 621 ff; (b) E. N. Jacobsen, M. H. Wu in: *Comprehensive Asymmetric Catalysis I–III* (Eds: E. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, **1999**, pp. 649 ff.

4 K. Drauz, H. Waldmann (Eds), *Enzyme Catalysis in Organic Synthesis*, Vols 1–3, 2nd edn, Wiley–VCH, Weinheim, **2002**.

5 For selected examples of recent patent applications, see: (a) M. J. O'Donnell, S. Wu, I. Esikova, A. Mi, US Pat. 5554753, **1996**; (b) E. N. Jacobsen, M. S. Sigman, PCT Int. Appl. WO 9951546, **1999**; (c) D. W. C. MacMillan, PCT Int. Appl. WO 2003002491, **2003**; (d) D. W. C. MacMillan, N. A. Paras, US Pat. 6784323, **2004**; (e) D. W. C. MacMillan, A. B. Northrup, PCI Int. Appl. WO 2003047740, **2003**; (f) D. W. C. MacMillan, K. A. Ahrendt, US Pat. 6307057, **2001**; (g) N. Halland, K. A. Jørgensen, T. Hansen, PCI Int. Appl. WO 20030619, **2003**; (h) K. Drauz, S. M. Roberts, T. Geller, A. Dhanda, US Pat. 6538105, **2003**; (i) K. Drauz, O. Burkhardt, S. M. Roberts, J. Skidmore, P. Coffey, US Pat. 6559283, **2003**; (j) K. Drauz, S. M. Roberts, J. Skidmore, US Pat. 6225482, **2001**; (k) S. M. Roberts, J. Skidmore, R. Flood, T. Geller, PCT Int. Appl. WO 2001094327, **2001**; (l) See Ref. [37]; (m) see Ref. [38]; (n) See Ref. [397]; (o) See Ref. [46]; (p) See Ref. [55]; (q) See Ref. [59]; (r) See Ref. [61].

6 A very interesting overview and discussion of criteria relevant to industrial catalytic processes is given in: H. U. Blaser, E. Schmidt in: *Asymmetric Catalysis on Industrial Scale* (Eds: H. U. Blaser, E. Schmidt) Wiley–VCH, Weinheim, **2004**, pp. 1 ff.

7 For selected examples, see: (a) K. A. Ahrendt, C. J. Borths, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2000**, *122*, 4243–4244; (b) A. B. Northrup, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2002**, *124*, 2458–2460; (c) W. S. Jen, J. J. M. Wiener, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2000**, *122*, 9874–9875.

8 For the pioneering work, see: (a) S. Julia, J. Masana, J. Vega, *Angew. Chem.* **1980**, *92*, 968–969; *Angew. Chem. Int. Ed. Engl.* **1980**, *19*, 929; (b) S. Julia, J. Guixer, J. Masana, J. Rocas, S. Colonna, R. Annuziata, H. Molinari, *J. Chem. Soc., Perkin Trans. 1* **1982**, 1317–1324.

9 W. Notz, F. Tanaka, S.-i. Watanabe, N. S. Chowdari, J. M. Turner, R. Thayumanavan, C. F. Barbas, III, *J. Org. Chem.* **2003**, *68*, 9624–9634.

10 K. Sakthivel, W. Notz, T. Bui, C. F. Barbas, III, *J. Am. Chem. Soc.* **2001**, *123*, 5260–5267.

11 M. S. Sigman, P. Vachal, E. N. Jacobsen, *Angew. Chem.* **2000**, *112*, 1336–1338; *Angew. Chem. Int. Ed. Engl.* **2000**, *39*, 1279–1281.

12 (a) S. S. Selkälä, J. Tois, P. M. Pihko, A. M. P. Koskinen, *Adv. Synth. Catal.* **2002**, *344*, 941–945; (b) K. Sakthivel, W. Notz, T. Bui, C. F. Barbas, III, *J. Am. Chem. Soc.* **2001**, *123*, 5260–5267.

13 For reviews, see: (a) B. List, *Synlett* **2001**, 1675–1686; (b) B. List, *Tetrahedron* **2002**, *58*, 5573–5590.

14 A. Berkessel, N. Gasch, K. Glaubitz, C. Koch, *Org. Lett.* **2001**, *3*, 3839–3842.

15 E. J. Corey, F. Xu, M. C. Noe, *J. Am. Chem. Soc.* **1997**, *119*, 12414–12415.

16 H.-g. Park, B.-S. Jeong, M.-S. Yoo, J.-H. Lee, M.-k. Park, Y.-J. Lee, M.-J. Kim, S.-s. Jew, *Angew. Chem.* **2002**, *114*, 3162–3164; *Angew. Chem. Int. Ed.* **2002**, *41*, 3036–3038.

17 (a) T. Ooi, M. Kameda, K. Maruoka, *J. Am. Chem. Soc.* **1999**, *121*, 6519–6520; (b) T. Ooi, M. Kameda, K. Maruoka, *J. Am. Chem Soc.* **2003**, *125*, 5139–5151.

18 H. Wack, A. E. Taggi, A. M. Hafez, W. J. Drury, III, T. Lectka, *J. Am. Chem. Soc.* **2001**, *123*, 1531–1532.

19 F.-Y. Zhang, E. J. Corey, *Org. Lett.* **2001**, *3*, 639–641.

20 M. S. Iyer, K. M. Gigstad, N. D. Namdev, M. Lipton, *J. Am. Chem.* **1996**, *118*, 4910–4911.

21 P. Vachal, E. N. Jacobsen, *J. Am. Chem. Soc.* **2002**, *124*, 10012–10013.

22 (a) B. List, *J. Am. Chem. Soc.* **2000**, *122*, 9336–9337; (b) B. List, P. Pojarliev, W. T. Biller, H. J. Martin, *J. Am. Chem. Soc.* **2002**, *124*, 827–833.

23 (a) A. Cordova, W. Notz, G. Zhong, J. M. Betancort, C. F. Barbas, III, *J. Am. Chem. Soc.* **2002**, *124*, 1842–1843; (b) W. Notz, F. Tanaka, S.-i. Watanabe, N. S. Chowdari, J. M. Turner, R. Thayumanavan, C. F. Barbas, III, *J. Org. Chem.* **2003**, *68*, 9624–9634.

24 (a) A. E. Taggi, A. M. Hafez, H. Wack, B. Young, W. J. Drury, III, T. Lectka, *J. Am. Chem. Soc.* **2000**, *122*, 7831–7832; (b) A. E. Taggi, A. M. Hafez, H. Wack, B. Young, D. Ferraris, T. Lectka, *J. Am. Chem. Soc.* **2002**, *124*, 6626–6635.

25 (a) B. List, R. A. Lerner, C. F. Barbas III, *J. Am. Chem. Soc.* **2000**, *122*, 2395–2396; (b) W. Notz, B. List, *J. Am. Chem. Soc.* **2000**, *122*, 7386–7387.

26 C. Pidathala, L. Hoang, N. Vignola, B. List, *Angew. Chem.* **2003**, *115*, 2891–2894; *Angew. Chem. Int. Ed.* **2003**, *42*, 2785–2788.

27 Y. Iwabuchi, M. Nakatani, N. Yokoyama, S. Hatakeyama, *J. Am. Chem. Soc.* **1999**, *121*, 10219–10220.

28 N. Kumaragurubaran, K. Juhl, W. Zhuang, A. Bogevig, K. A. Jørgensen, *J. Am. Chem. Soc.* **2002**, *124*, 6254–6266.

29 S. P. Brown, M. P. Brochu, C. J. Sinz, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2003**, *125*, 10808–10809.

30 G. Zhong, *Angew. Chem.* **2003**, *115*, 4379–4382.

31 (a) Y. Hayashi, J. Yamaguchi, K. Hibino, M. Shoji, *Tetrahedron Lett.* **2003**, *44*, 8293–8296; (b) A. Bøgevig, H. Sunder, A. Cordova, *Angew. Chem. Int. Ed.* **2004**, *43*, 1109–1112.

32 W. S. Jen, J. J. M. Wiener, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2000**, *122*, 9874–9875.

33 I.-D. Hills, G. C. Fu, *Angew. Chem.* **2003**, *115*, 4051–4054; *Angew. Chem. Int. Ed.* **2003**, *42*, 3921–3924.

34 For reviews, see: (a) C. Lauret, S. M. Roberts, *Aldrichim. Acta* **2002**, *35*, 47–51; (b) T. Geller, A. Gerlach, C. M. Krüger, H. C. Militzer, *Chim. Oggi* **2003**, *21*(9), 6–8.

35 B. E. Bosch, *Chiral Europe 2004 Conference Proceedings*, Scientific Update Conferences, Mainz, June 14–16, **2004**.

36 T. Geller, A. Gerlach, C. M. Krüger, H.-C. Militzer, *Tetrahedron Lett.* **2004**, *45*, 5065–5067.

37 T. Geller, C. M. Krüger, H.-C. Militzer, EP Pat. 1279670, **2004**.

38 T. Geller, C. M. Krüger, H.-C. Militzer, US Pat. 6770766, **2004**.

39 T. Geller, C. M. Krüger, H.-C. Militzer, DE Pat. 10136132, **2003**.

40 T. Geller, C. M. Krüger, H.-C. Militzer, *Tetrahedron Lett.* **2004**, *45*, 5069–5071.

41 S. B. Tsogoeva, J. Wöltinger, C. Jost, D. Reichert, A. Kühnle, H.-P. Krimmer, K. Drauz, *Synlett* **2002**, 707–710.

42 (a) C. Wandrey, E. Flaschel, *Adv. Biochem. Eng.* **1979**, *12*, 147–218;

(b) C. Wandrey, W. Leuchtenberger, M.-R. Kula, US 4304858, **1981**; (c) A. S. Bommarius, K. Drauz, H. Klenk, C. Wardrey, *Enzyme Eng. 11 Ann. N.Y. Acad. Sci.* **1992**, 1269; (d) A. S. Bommarius in: *Biotechnology* (Eds.: H.-J. Rehm, G. Reed, A. Pühler, P. Stadler), Vol. 3, 1993, VCH, Weinheim, p. 4271; (e) H. Gröger, K. Drauz in: *Asymmetric Catalysis on Industrial Scale* (Eds: H. U. Blaser, E. Schmidt), **2004**, VCH, Weinheim, Section 1.8, pp. 131–147.

43 D. Ager, *8th International Conference on Organic Process Research and Development*, Conference presentation, Scientific Update Conference, Barcelona, September 7–10, **2003**.

44 M. S. Sigman, E. N. Jacobsen, *J. Am. Chem. Soc.* **1998**, *120*, 4901–4902.

45 M. S. Sigman, E. N. Jacobsen, *Book of Abstracts, 216th ACS Meeting*, Boston, August 23–27, **1998**.

46 E. N. Jacobsen, M. S. Sigman, PCT Int. Appl. WO 9951546, **1999**.

47 M. S. Sigman, P. Vachal, E. N. Jacobsen, *Angew. Chem.* **2000**, *112*, 1336–1338; *Angew. Chem. Int. Ed. Engl.* **2000**, *39*, 1279–1281.

48 P. Vachal, E. N. Jacobsen, *Org. Lett.* **2000**, *2*, 867–870.

49 http://www.rhodiachirex.com/techpages/amino_acid_technology.htm

50 For an excellent review about process research at Merck, see: E. J. J. Grabowski, *ACS Symposium Series* **2004**, *870* (Chemical Process Research), 1–21.

51 U.-H. Dolling, P. Davis, E. J. J. Grabowski, *J. Am. Chem. Soc.* **1984**, *106*, 446–447.

52 D. L. Hughes, U.-H. Dolling, K. M. Ryan, E. F. Schoenewaldt, E. J. J. Grabowski, *J. Org. Chem.* **1987**, *52*, 4745–4752.

53 For excellent recent reviews, see: (a) M. J. O'Donnell, *Aldrichim. Acta* **2001**, *34*, 3–15; (b) M. J. O'Donnell, *Acc. Chem. Res.* **2004**, *38*, 506–517.

54 M. J. O'Donnell, W. D. Bennett, S. Wu, *J. Am. Chem. Soc.* **1989**, *111*, 2353–2355.

55 S. S. Jew, H. G. Park, B. S. Jeong, M. S. Yoo, S. H. Lee, WO 2002083670, **2002**.

56 H.-g. Park, B.-S. Jeong, M.-S. Yoo, J.-H. Lee, M.-k. Park, Y.-J. Lee, M.-J. Kim, S.-s. Jew, *Angew. Chem.* **2002**, *114*, 3162–3164; *Angew. Chem. Int. Ed.* **2002**, *41*, 3036–3038.

57 S.-s. Jew, B.-S. Jeong, M.-S. Yoo, H. Huh, H.-g. Park, *Chem. Commun.* **2001**, 1244–1245.

58 H.-g. Park, B.-S. Jeong, M.-S. Yoo, M.-k. Park, H. Huh, S.-s. Jew, *Tetrahedron Lett.* **2001**, *42*, 4645–4648.

59 S. S. Jew, H. G. Park, B. S. Jeong, M. S. Yoo, S. H. Lee, D. H. Cho, WO 2003045948, **2003**.

60 H.-g. Park, personal communication.

61 (a) G. K. Mulholland, M. J. O'Donnell, F. T. Chin, F. Delgado, WO 2002044144, **2002**; (b) K. Fujita, Y. Taguchi, A. Oishi, JP 3459986, **2003**.

62 Z. G. Hajos, D. R. Parrish, DE 2102623, **1971**.

63 Z. G. Hajos, D. R. Parrish, *J. Org. Chem.* **1974**, *39*, 1612–1615.

64 Z. G. Hajos, D. R. Parrish, *J. Org. Chem.* **1974**, *39*, 1615–1621.

65 U. Eder, G. Sauer, R. Wiechert, *Angew. Chem.* **1971**, *83*, 492–493; *Angew. Chem. Int. Ed. Engl.* **1971**, *10*, 496–497.

66 U. Eder, R. Wiechert, G. Sauer, DE 2014757, **1971**.

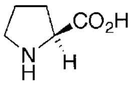
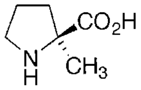
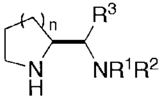
67 E. Ottow, personal communication.

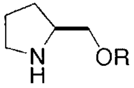
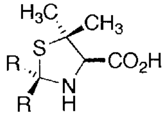
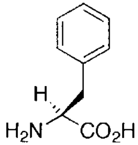
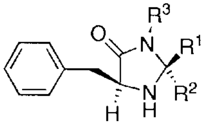
Appendix: Tabular Survey of Selected Organocatalysts: Reaction Scope and Availability

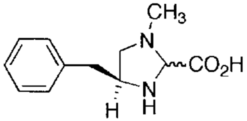
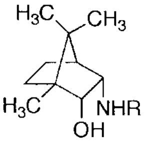
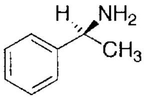
The appendix lists typical examples of organocatalysts together with their reaction scope, the chapters where their application is discussed, and some information on their availability.

Asymmetric Organocatalysis. Albrecht Berkessel and Harald Gröger
Copyright © 2005 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim
ISBN: 3-527-30517-3

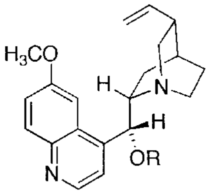
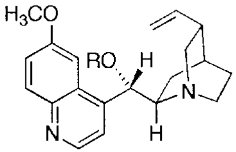
I
Primary and Secondary Amine Catalysts

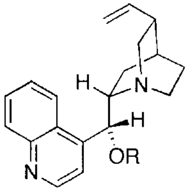
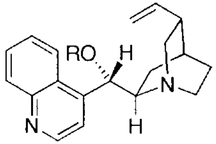
Structure	***Typical reaction scope [chapter]***	***Availability***
 L-proline	• Intermolecular Michael addition [4.1] • Mannich reaction [5.2] • Intermolecular aldol reaction [6.2.1] • Intramolecular aldol reaction [6.2.2] • Aldol-related reactions (addition of nitrones) [6.2.3] • Addition to N=N double bonds (α-amination of carbonyl compounds) [7.1] • Addition to N=O double bonds (α-aminoxylation/ hydroxylation of carbonyl compounds [7.2]	L-Proline is commercially available in bulk quantities and represents an economically attractive amino acid organocatalyst. (D-Proline is commercially available, too.)
 α-methyl-L-proline	• Intramolecular α-alkylation of aldehydes [3.3]	L-Enantiomer commercially available
 n = 1,2 L-proline-derived diamines (and homologues)	• Intermolecular Michael addition [4.1] • Intermolecular aldol reaction [6.2.1] • [3+2]-Cycloadditions [8.2] • Desymmetrization of *meso*-diols [13.3] • Desymmetrization of *meso*-epoxides [13.4]	Preparation starting from L-proline in multi-step syntheses

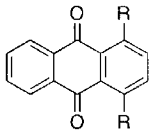
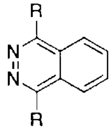
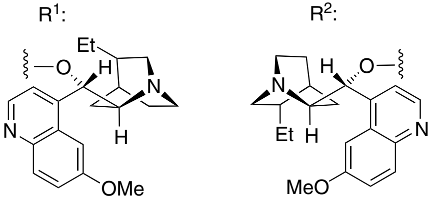
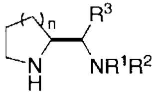
 L-proline-derived amino ethers	• Mannich reaction [5.2]	Preparation starting from L-proline in multi-step syntheses
 L-4-thiazolidinyl carboxylic acid	• Mannich reaction [5.2] • Intermolecular aldol reaction [6.2.1]	Readily accessible, using L-penicillamine as starting material
 L-phenylalanine	• Intramolecular aldol reaction [6.2.2]	Just as L-proline, L-phenylalanine is an economically attractive amino acid organocatalyst, readily available in bulk quantities.
 L-Phe-derived imidazolidinones	• Intermolecular Michael addition, including alkylation of heterocyclic aromatics and aniline derivatives [4.1] • [4+2]-Cycloadditions: Diels-Alder reactions [8.1] • [3+2]-Cycloadditions: Nitrone-based reactions [8.2]	Organocatalysts readily prepared from L-phenylalanine, methylamine and acetone or piraldehyde

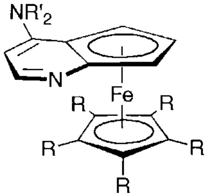
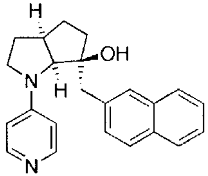
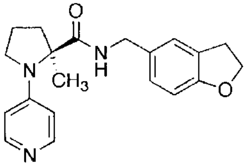
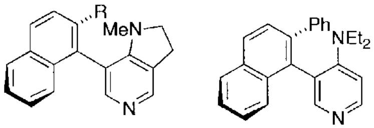
Structure	***Typical reaction scope [chapter]***	***Availability***
	• Intermolecular Michael addition [4.1]	Prepared from L-phenylalanine, methylamine and glyoxylic acid in a few steps
	• Tautomerization of enols [9]	Prepared from (+)-camphor in a multi-step syntheses
	• Intramolecular Michael addition [4.2]	Commercially available in both enantiomeric forms in bulk quantities; economically attractive organocatalyst

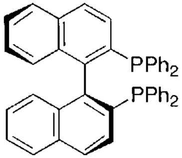
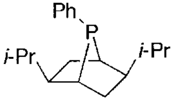
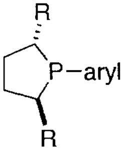
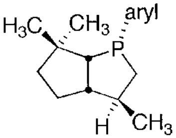
II
Tertiary Amine and Pyridine Catalysts

Structure	***Typical reaction scope [chapter]***	***Availability***
 (-)-quinine (R = H)  (+)-quinidine (R = H)	• α-Halogenation of carbonyl compounds [3.4] • Intermolecular Michael addition (including cyclopropanation of enones, enoates etc.) [4.1] • Intramolecular Michael addition [4.2] • β-Lactam synthesis from imines and ketenes [5.3] • β-Lactone synthesis from aldehydes and ketenes [6.3] • Morita-Baylis-Hillman reaction [6.4] • Hydrophosphonylation of aldehydes [6.10] • Diels-Alder reaction [8.1] • Desymmetrization of *meso*-anhydrides [13.1]	All four natural cinchona alkaloids (R=H) are commercially available in large quantities.

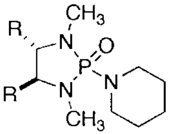
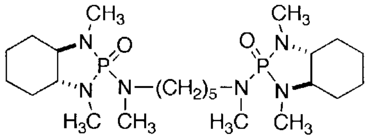
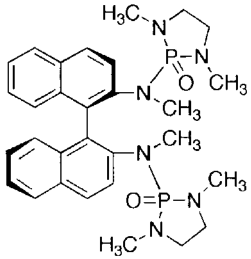
Structure	***Typical reaction scope [chapter]***	***Availability***
 (-)-cinchonidine (R = H)  (+)-cinchonine (R = H) Cinchona alkaloids	• Additions to prochiral ketenes [13.2] • Desymmetrization of *meso*-diols [13.3] • Desymmetrization of *meso*-epoxides [13.4]	

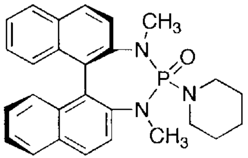
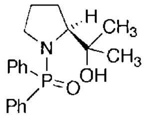
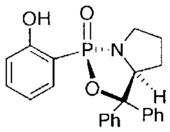
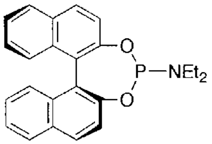
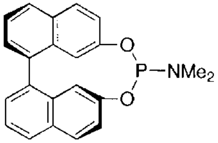
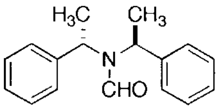
[(DHQD)$_2$AQN], R = R^1 [(DHQ)$_2$AQN], R = R^2  [(DHQD)$_2$PHAL], R = R^1 [(DHQ)$_2$PHAL], R = R^2   dimeric cinchona alkaloid derivatives	• α-Halogenation of carbonyl compounds [3.4] • Carboethyoxycyanation of ketones [6.1] • Desymmetrization of *meso*-anhydrides [13.1] • (Dynamic) kinetic resolution of racemic anhydrides [13.1]	Commercially available
 n = 1,2 L-proline-derived diamines	• Kinetic resolution of racemic alcohols by acylation [12.1] • Desymmetrization of *meso*-diols by acylation [13.3]	Preparation starting from L-proline in multi-step syntheses

Structure	*Typical reaction scope [chapter]*	*Availability*
	• *β*-Lactam synthesis from imines and ketenes [5.3] • Kinetic resolution of racemic alcohols by acylation [12.1] • Additions to prochiral ketenes [13.2] • Desymmetrization of *meso*-diols [13.3] • Dynamic kinetic resolution of azlactones; rearrangement of *O*-acyl azlactones, *O*-acyl oxindoles, *O*-acyl benzofuranones [13.6]	Multistep synthesis
	• Kinetic resolution of racemic alcohols by acylation [12.1]	Multistep synthesis
	• Kinetic resolution of racemic alcohols by acylation [12.1]	Multistep synthesis

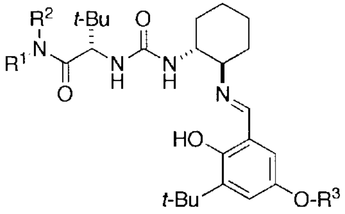
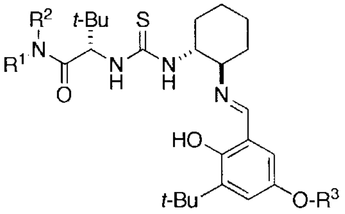
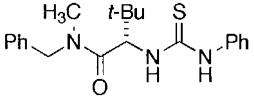
Structure	*Typical reaction scope [chapter]*	*Availability*
 BiNAP	• Morita-Baylis-Hillman reaction [6.4]	Commercially available in large quantities
	• [3+2]-Cycloadditions of allenes [8.2]	Multistep synthesis
	• Kinetic resolution of racemic alcohols by acylation [12.1] • Desymmetrization of *meso*-diols [13.3]	Few steps from chiral diols
	• Kinetic resolution of racemic alcohols by acylation [12.1] • Desymmetrization of *meso*-diols [13.3]	Multistep synthesis

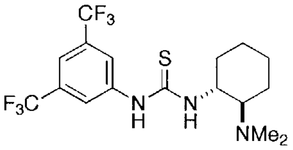
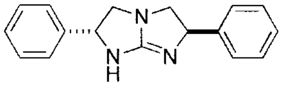
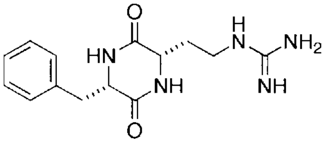
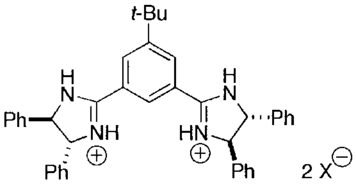
IV
Phosphoramidites, Phosphoramides and Formamides

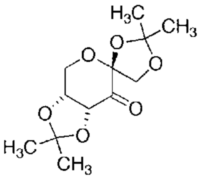
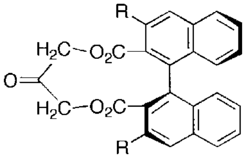
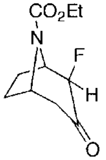
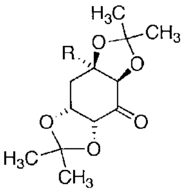
Structure	***Typical reaction scope [chapter]***	***Availability***
	• Intermolecular aldol reaction [6.2.1] • Allylation of aldehydes [6.5]	Prepared from chiral diamines, e.g. commercially available cyclohexane-1,2-diamine, in a few steps
 and analogues thereof	• Allylation of aldehydes [6.5]	Prepared from chiral diamines, e.g. commercially available cyclohexane-1,2-diamine, in a few steps
	• Allylation of aldehydes [6.5]	Prepared from commercially available BINAM in a few steps

 and dimers thereof	• Intermolecular aldol reaction [6.2.1] • Desymmetrization of *meso* epoxides [13.4]	Prepared from commercially available BINAM in a few steps
   	• Reduction of carbonyl compounds with boranes [11.1]	Readily available from BINOL and prolinol derivatives, respectively
	• Allylation of aldehydes [6.5]	Readily available by formylation of commercially available bis(phenethyl)amine

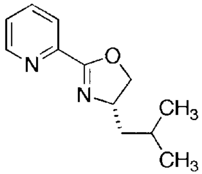
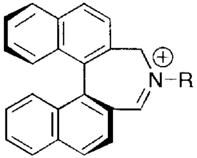
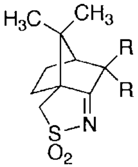
V
Ureas, Thioureas, Guanidines, Amidines

Structure	***Typical reaction scope [chapter]***	***Availability***
	• Hydrocyanation of imines [5.1]	Multi-step synthesis using enantiomerically pure trans-1,2-diaminocyclohexane and *tert.*-leucine
	• Hydrocyanation of imines [5.1] • Mannich reaction [5.2] • Hydrophosphonylation of imines [5.5]	Multi-step synthesis using enantiomerically pure trans-1,2-diaminocyclohexane and *tert.*-leucine; immobilization possible
	• Mannich reaction [5.2]	Few steps from *tert*-leucine

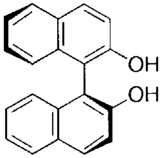
	• Intermolecular Michael addition [4.1] • Aza-Henry reaction [5.2]	Few steps from ennantiomerically pure trans-1,2-diaminocyclohexane
	• Hydrocyanation of imines [5.1]	Multi-step synthesis
	• Hydrocyanation of imines [5.1] • Hydrocyanation of aldehydes [6.1]	Few synthetic steps from L-phenylalanine and L-nor-arginine
	• [4+2]-Cycloadditions, Diels-Alder reactions [8.1]	Multi-step synthesis

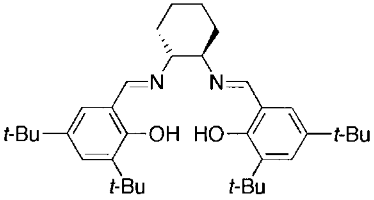
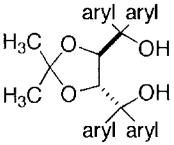
Structure	***Typical reaction scope [chapter]***	***Availability***
 and related carbohydrate derivatives	• Epoxidation of olefins [10.1] • kinetic resolution of alcohols by oxidation [10.4; 12.2]	Readily prepared from D-fructose in two steps
	• Epoxidation of olefins [10.1]	Multi-step synthesis
	• Epoxidation of olefins [10.1]	Prepared from commercially available N-carboethoxytropinone in a few steps
	• Epoxidation of enones and enoates [10.2]	Prepared from commercially available (−)-quinic acid in a few steps

VII
Imines, Iminium Cations and Oxazolines

Structure	*Typical reaction scope [chapter]*	*Availability*
	• Allylation of aldehydes [6.5]	Readily prepared from L-leucinol and pyridine-2-carboxylic acid
	• Epoxidation of olefins [10.1]	Multi-step synthesis
	• Sulfoxidation of thioethers [10.3]	Prepared from commercially available (+)-camphor-10-sulphonic acid in a few steps

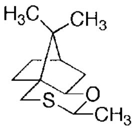
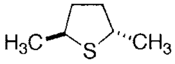
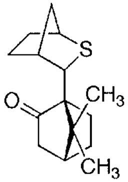
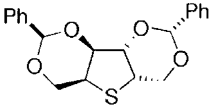
VIII
Diols

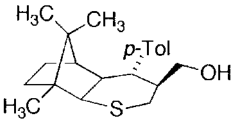
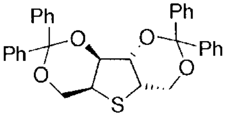
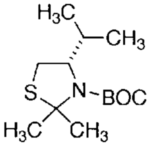
<table>
<tr><th>Structure</th><th>Typical reaction scope [chapter]</th><th>Availability</th></tr>
<tr><td>

BINOL and derivatives thereof</td><td>• Hydrocyanation (using TMS-CN) of aldehydes [6.1]
• Morita-Baylis-Hillman-reaction [6.4]
• Reduction of carbonyl compounds [11.3]</td><td>BINOL is commercially available in both enantiomeric forms</td></tr>
<tr><td>
</td><td>• Hydrocyanation (using TMS-CN) of aldehydes [6.1]</td><td>Commercially available</td></tr>
<tr><td>

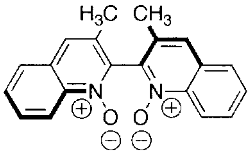
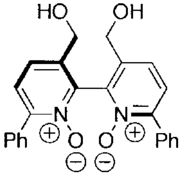
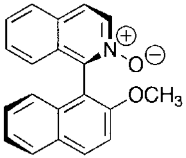
TADDOLs</td><td>• Hetero-Diels-Alder-reaction [8.1]</td><td>Readily available from (+)- or (−)-tartaric acid; some TADDOLs are commercially available</td></tr>
</table>

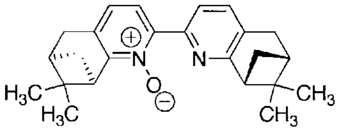
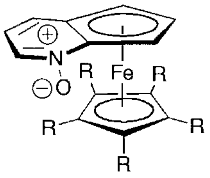
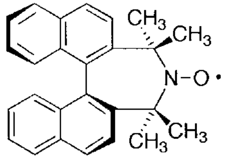
IX
Sulfides

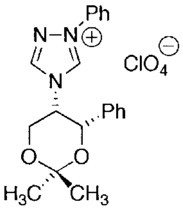
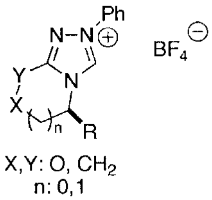
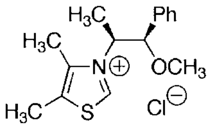
Structure	*Typical reaction scope [chapter]*	*Availability*
	• Aziridination of imines [5.4] • Epoxidation of aldehydes [6.8]	Prepared from commercially available (+)-camphor-10-sulfonic acid in a few steps
	• Aziridination of imines [5.4] • Epoxidation of aldehydes [6.8]	Prepared in few steps from commercially available hexane-2,5-diol
	• Aziridination of imines [5.4] • Epoxidation of aldehydes [6.8]	Prepared from commercially available (+)-camphor-10-sulfonic acid
	• Morita-Baylis-Hillman-reaction [6.4] • Epoxidation of aldehydes [6.8]	Three-step synthesis starting from D-mannitol

Structure	***Typical reaction scope [chapter]***	***Availability***
	• Epoxidation of aldehydes [6.8]	Multi-step synthesis
	• Epoxidation of aldehydes [6.8]	Three-step synthesis starting from D-mannitol
	• Epoxidation of aldehydes [6.8]	Multi-step synthesis from L-valine

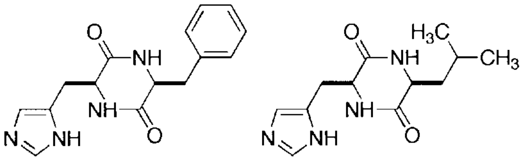
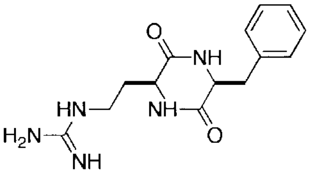
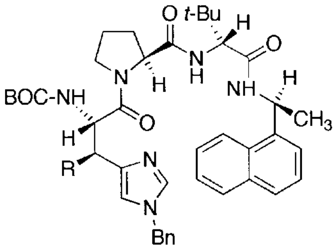
X
N-Oxides and Nitroxyl Radicals

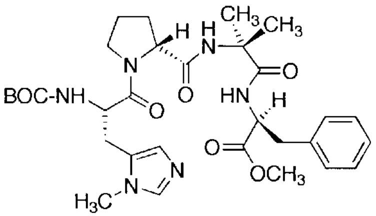
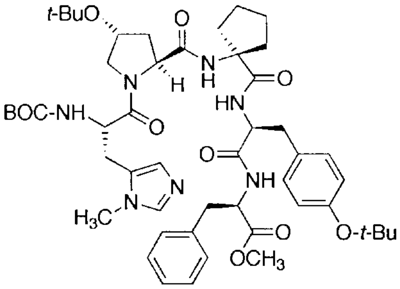
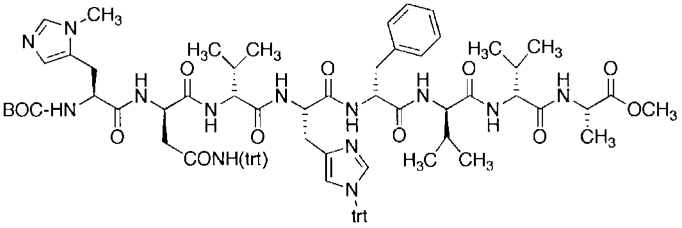
Structure	*Typical reaction scope [chapter]*	*Availability*
	Hydrocyanation of imines (Strecker reaction) [5.1] Allylation of aldehydes [6.5]	Multi-step synthesis
	Allylation of aldehydes [6.5]	Multi-step synthesis
	Allylation of aldehydes [6.5]	Multi-step synthesis

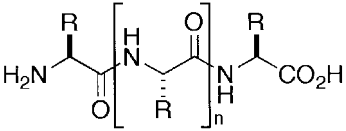
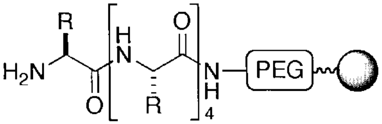
Structure	***Typical reaction scope [chapter]***	***Availability***
	Allylation of aldehydes [6.5]	Multi-step synthesis
	Desymmetrization of *meso*-epoxides [13.4]	Multi-step synthesis
	Kinetic resolution of alcohols by oxidation [10.4; 12.2]	Multi-step synthesis

Structure	Typical reaction scope [chapter]	Availability
	• Benzoin condensation [6.9]	Several synthetic steps from commercial chiral aminodiol
	• Benzoin condensation [6.9]	Several synthetic steps from e.g. L-*tert.*-leucinol
	• Stetter-reaction [6.9]	Several synthetic steps from (−)-norephedrine

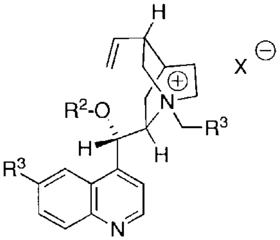
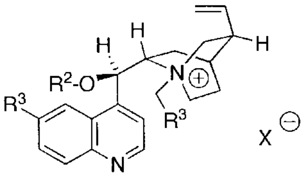
XII
Peptides

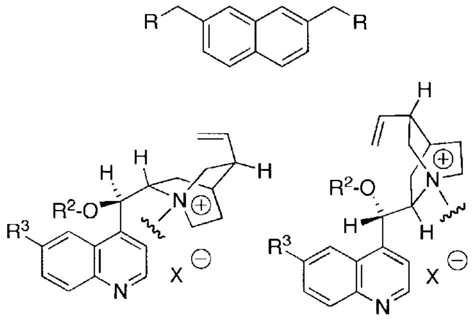
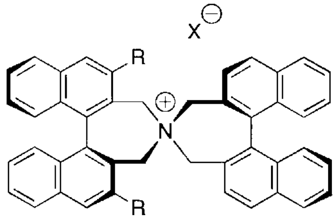
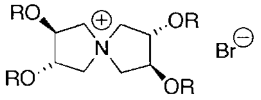
Structure	*Typical reaction scope [chapter]*	*Availability*
	• Hydrocyanation of aldehydes [6.1]	Readily available from commercial amino acids
	• Hydrocyanation of imines [5.1]	Readily available from commercial amino acids
 example for tripeptide catalyst	• Intermolecular Michael addition of TMS azide [4.1.2] • Kinetic resolution of alcohols by acylation [12.1]	Synthesis by several peptide coupling steps (plus synthesis of β-alkylated histidine, if desired)

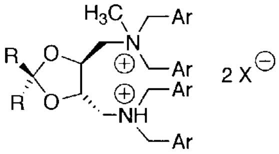
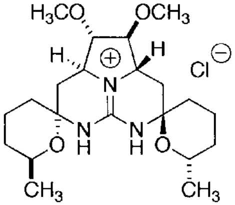
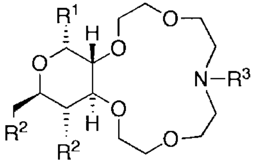
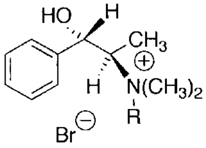
 example for tetrapeptide catalyst	• Kinetic resolution of alcohols by acylation [12.1]	Several peptide coupling steps
 example for pentapeptide catalyst	• Kinetic resolution of alcohols by acylation [12.1] • Desymmetrization of *meso*-diols [12.1, 13.3]	Several peptide coupling steps
 example for octapeptide catalyst	• Kinetic resolution of alcohols by acylation [12.1]	Several peptide coupling steps

Structure	***Typical reaction scope [chapter]***	***Availability***
 poly-L-amino acid	• Epoxidation of enones [10.2]	Readily available by polymerization of e.g. amino acid N-carboxy anhydrides
 R: *iso*-butyl L-leucine pentamer on TentaGel S NH_2	• Epoxidation of enones with short solid-phase bound peptides [10.2]	Readily available by peptide synthesis on solid phase

XIII
Phase Transfer Catalysts

Structure	*Typical reaction scope*	*Availability*
  general structures of N-alkylated cinchona alkaloids	• Alkylations with formation of C–C bonds [3.1, 3.2] • Halogenation [3.4] • Intermolecular Michael addition [4.1] • Intermolecular aldol reaction [6.2.1] • Intramolecular aldol reaction [6.2.2] • Aldol-related reactions (e.g. vinylogous Mukaiyama-type aldol) [6.2.3] • Alkylation of C=O double bonds [6.6] • Darzens reaction [6.7] • Epoxidation of enones [10.2] • Reduction of carbonyl compounds [11] • Horner-Wadsworth-Emmons reaction [13.5]	The starting materials for the synthesis (few steps) of these phase-transfer catalysts, i.e. the cinchona alkaloids (−)-quinine, (+)-quinidine, (+)-cinchonine and (−)-cinchonidine, are commercially available in large quantities.

Structure	***Typical reaction scope***	***Availability***
 dimeric alkaloid-based phase-transfer catalysts	• Alkylations with formation of C–C bonds [3.1, 3.2] • Halogenations with formation of C–X bonds [3.4] • Intermolecular Michael addition [4.1] • Epoxidation of enones [10.2]	See section above.
 Biaryl-derived phase-transfer catalysts	• Alkylations with formation of C–C bonds [3.1, 3.2] • Intermolecular Michael additions [4.1] • Intermolecular aldol reaction [6.2.1] • Epoxidation of enones [10.2]	Multi-step synthesis from commercially available binaphthyls.
	• Intermolecular Michael addition [4.1]	Multi-step synthesis

 Tartrate-based dicationic phase-transfer catalysts	• Alkylations with formation of C–C bonds [3.1, 3.2] • Intermolecular Michael addition [4.1]	Few steps from commercially available (+)- or (−)-tartaric acid
	• Alkylations with formation of C–C bonds [3.1, 3.2]	Multi-step synthesis
 Carbohydrate-derived crown ethers	• Intermolecular Michael addition [4.1] • Darzens reaction [6.7]	Multi-step synthesis
 R: alkyl or solid-phase attachment	• Darzens reaction [6.7]	Few steps from commercially available amino alcohols such as ephedrin

Index

a
Alcohols
– by alkylation of carbonyl compounds 205
– by ketone reduction 314
– by kinetic resolution
– – by acylation 323
– – by oxidaton 306, 342
Aldol reaction
– 6-enolexo aldolization 174
– crossed-aldol reaction of aldehydes 148, 156
– catalysts
– – carbocations 146
– – diamines 153
– – guanidines 177
– – phosphamides 141, 155
– – phase-transfer-catalysts 145, 159, 162, 176
– – proline and related amino acids 147, 161
– direct aldol reactions 147, 161
– indirect aldol reactions 140, 154
– intermolecular aldol reaction 140
– intramolecular aldol reaction 166, 405
– mechanism
– – of proline catalysis 151, 164, 171
– – of phosphoramide catalysis 145
– nitroaldol reaction 176
– nitrone addition to ketones 178
– nucleophiles in aldol reactions
– – aldehyes 150, 174
– – amino acid imines 159, 162
– – enol ethers 140, 160
– – ketones 147, 161, 166
– self-aldolization of aldehydes 150
– vinylogous aldol reaction 175
Alkaloids
– as chiral bases
– – hydrophosphonylation of aldehydes 235
– – Michael-addition of C-nucleophiles to α,β-unsaturated carbonyl compounds 48, 78
– – Michael-addition of O-nucleophiles to α,β-unsaturated carbonyl compounds 79
– – Michael-addition of S- and Se- nucleophiles to α,β-unsaturated carbonyl compounds 74
– as nucleophilic catalysts
– – addition of alcohols to ketenes 270, 363
– – desymmetrization of *meso*-anhydrides 349
– – desymmetrization of *meso*-diols 367
– – kinetic/dynamic kinetic resolution of racemic anhydrides 352, 358
– – β-lactam synthesis 109
– – β-lactone synthesis 180
– – trifluoromethylation of aldehydes 205
– – and ketones
– as phase-transfer-catalysts
– – aldol reactions 145, 159
– – alkylation of amino acid imines 16, 403
– – alkylation of ketones 13, 205, 402
– – Darzens-reaction 206
– – epoxidation of enones 299
– – Michael-additions 47
– – reduction of ketones 318
Alkylation
– of aldehydes and ketones 205
– α-alkylation of aldehydes, intramolecular 33
– of benzene derivatives by enals 60
– α-alkylation of β,γ-enoates 33
– α-alkylation of ketones 13, 402
Alkylidene malonates
– Michael-acceptors 67
Allylation
– of aldehydes by allyl silanes 190
– catalysts for allylation of aldehydes
– – phosphoramides 190
– – N-oxides 190
Amidinium cations
– catalysts for Diels-Alder-reaction 263

Asymmetric Organocatalysis. Albrecht Berkessel and Harald Gröger
Copyright © 2005 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim
ISBN: 3-527-30517-3

Amination
– α-amination of aldehydes and ketones 69, 245
Amines
– as catalysts for
– – aldol reactions 153
– – desymmetrization of *meso*-anhydrides 358
– – desymmetrization of *meso*-diols 369
– – desymmetrization of *meso*-epoxides 374
– – kinetic resolution of alcohols 326
– – Morita-Baylis-Hillman-reaction 183
β-Amino acid esters 106
α-Amino acids
– by alkylation of glycine imines 16, 30, 52
– by α-amination of aldehydes 69, 245
– by Strecker-reaction 85, 401
– α,α-disubstituted α-amino acids 28, 92
– β-hydroxy α-amino acid derivatives 159
– non-natural α-amino acids 25, 402
– solid phase synthesis of 31
α-Aminoxylation
– of aldehydes and ketones 249
Anhydrides
– desymmetrization of *meso*-anhydrides 349
– kinetic/dynamic kinetic resolution of racemic anhydrides 352, 358
Azides
– conjugate addition of azide to enimides 72
Aziridination
– of imines 119
Azlactones
– dynamic kinetic resolution by alcoholysis 387
– O-acyl azlactones, enantioselective rearrangement of 385
Azodicarboxylates
– Michael-acceptors 69, 245

b
Baylis-Hillman reaction
– See Morita-Baylis-Hillman reaction
Benzoin condensation 227
BINOL and derivatives
– cyanide addition to aldehydes 136
– Morita-Baylis-Hillman-reaction 186
α-Bromination of acyl derivatives 38

c
α-Chlorination of acyl halides/esters 38
Crown ethers
– phase-transfer-catalysts
– – Darzens-reaction 207
Cyanohydrins 130
Cycloadditions
– [3+2]-cycloadditions 262
– [4+2]-cycloadditions 256
Cyclopropanation
– of enoates, by phenacyl halides 70

d
Darzens-reaction 205
Desymmetrization
– of *meso*-anhydrides 349
– of *meso*-diols 367
– of *meso*-epoxides
– – by isomerisation to allylic alcohols 374
– – by ring opening, addition of nucleophiles 381
Diels-Alder-reaction
– catalysis by chiral bases 257
– catalysis by amidinium cations 263
– catalysis by imidazolidinones 258
Diketopiperazine catalysts
– for the hydrocyanation of aldehydes 131
– for the Strecker-reaction 85
Dimeric cinchona alkaloid catalysts
– for cyanide addition to ketones 136
– for kinetic/dynamic kinetic resolution of anhydrides 352, 358
– for the Michael-addition of S-nucleophiles 77
Diols
– kinetic resolution, desymmetrization
– – by acylation 335, 367
– – by oxidation 306, 343, 374
Dioxiranes catalysts
– epoxidation
– – of enones and enoates 290
– – of enol ethers 283
– – of olefins 277
– oxidation of alcohols, diols 306
DMAP-based nucleophilic catalysts
– chiral DMAP-derivatives
– – addition of alcohols to ketenes 329, 363
– – addition of pyrroles to amines 365
– – dynamic kinetic resolution of azlactones 387
– – isomerization of O-acyl azlactones 385
– – kinetic resolution of alcohols 327
– – kinetic resolution of amines 340
– – β-lactam synthesis 118

e
Economy of organocatalysts 394
Enals
– as Michael-acceptors 58
Enones
– as Michael-acceptors 56, 63

Epoxidation of
– aldehydes 211
– alkenes 277
– enones/enoates 290, 398

f
Flavins
– sulfoxidation of thioethers 305
α-Fluorination of ketones, enol ethers 34
Formamides
– catalysts
– – for allylation of aldehydes 198

g
Guanidine-based catalysts
– for modified aldol reactions 176
– for the Strecker reaction 86

h
Henry reaction
– see Nitroaldol reaction
High pressure
– in direct aldol reaction 151
– in modified aldol reaction 176
Horner-Wadsworth-Emmons reaction 383
Hydrocyanation
– of aldehydes 130
– of imines (Strecker-reaction) 85, 401
Hydrophosphonylation
– of aldehydes 234
– of imines 126
β-Hydroxy carboxylic acid esters 142
β-Hydroxy carbonyl compounds
– by aldol reaction 140
– by Morita-Baylis-Hillman reaction 182
α-Hydroxylation
– of aldehydes and ketones 249

i
Imidazolidinones
– catalysts for
– – Diels-Alder-reactions 259
– – Michael-additions 58, 63
– – Mukaiyama-Michael-reactions 61
– – nitrone [3+2]-cycloadditions 262
Imines
– catalysts for
– – sulfoxidation of thioethers 303
– – Mannich-reaction 107
– – Strecker-reaction 89
– Substrates for
– – Aziridination 119
– – hydrocyanation reaction (Strecker-reaction) 85
– – β-Lactam synthesis 109
– – Mannich-reaction 97
Iminium ions
– catalysts for epoxidation of olefins 287
– intermediates in
– – aldol reaction 152
– – Diels-Alder-reaction of enals 261
– – Michael-additions 56
Immobilization
– immobilized catalysts 395
– of ephedrinium salt 207
– of imidazolidinones 260, 395
– of L-proline 151, 396
– of short-chain peptides 297, 396
– of thiourea catalysts 90, 395
Indoles
– conjugate addition to enals 59

k
Ketenes
– addition of alcohols to ketenes 270, 329, 363
– in β-lactam synthesis 109
Ketones
– direct aldol reaction with 147, 161
– direct Mannich reaction with 97
– chiral ketones as catalysts for the epoxidation of
– – enones/enoates 290
– – alkenes 278
– Michael addition with 50
– trifluoromethylation of 205
Kinetic resolution
– of amines 340
– of alcohols
– – by acylation 323
– – by oxidation 306, 343

l
Large-scale applications 393
β-Lactam synthesis
– from imines and ketenes 109
β-Lactone synthesis
– via addition to ketenes 179
– via aldol reaction of carboxy aldehydes 167

m
Mannich-reaction 97
– catalysts for
– – binaphthyl phosphoric acid 106, 108
– – β-amino alcohols 105
– – diamines 99
– – proline and related amino acids 97
– – pyrrolidinyltetrazole 106

– – thioureas 106
– nucleophiles as substrates
– – ketones 97
– – silyl ketene acetals 106
Michael-addition
– of C-nucleophiles 47, 78
– of N-nucleophiles 71
– of O-nucleophiles 79
– of S-nucleophiles 73
– of Se-nucleophiles 76
Morita-Baylis-Hillman-reaction 182
Mukaiyama-Michael-addition to enals 61

n
N-heterocyclic carbenes
– as nucleophilic catalysts for the benzoin-condensation 230
Nitroaldol reaction 176
Nitroolefins
– as Michael-acceptors 65, 68
Nitrones
– in modified aldol reactions 178
– in [3+2]-cycloadditions 262
Nitrosobenzene
– α-aminoxylation of aldehydes and ketones 249
Nitroxyl radicals
– catalysts for alcohol oxidation 306, 343
N-Oxide catalysts
– allylation of aldehydes 190, 199
– epoxide ring opening 381
– Strecker-reaction 95
N-Sulfonyloxaziridines
– sulfoxidation of thioethers 304

o
O-acyl benzofurans, enantioselective rearrangement of 388
O-acyl oxindoles, enantioselective rearrangement of 388

p
Peptide catalysts
– conjugate addition of azide 72
– desymmetrization of diols/polyols 340
– epoxidation of enones 290
– kinetic resolution of alcohols 335
Phase-transfer catalysis
– alkylation of amino acid imines 16
– alkylation of ketones 205
– Darzens-reaction 206
– epoxidation of enones 299
– Michael-additions 47
Phase-transfer catalysts
– alkaloids 13, 17, 29, 48, 318
– binaphthyl derivatives 21, 29, 49
– crown ethers 55
– guanidinium cations 24
– tartaric acid derivatives 23, 28, 53
Phosphoramides
– catalysts for
– – aldol reaction 140, 154
– – allylation of aldehydes 190
– – epoxide ring opening 382
Phosphazene bases 32
– immobilized 40
Phosphines
– catalysts for
– – Morita-Baylis-Hillman-reaction 186
– – cycloaddition of 2, 3-butadienoates to acrylates 267
– – desymmetrization of *meso*-diols 368
– – kinetic resolution of alcohols 323
Proline
– catalyst for aldol-reactions 147, 163, 168, 405
– catalyst for the Mannich-reaction 97
– catalyst for Michael-additions 56
Protonation
– asymmetric, of enolates 269, 274
Pyrroles
– conjugate addition to enals 58

q
Quinones, epoxidation of 299

r
Reduction
– of ketones
– – by boranes, CBS-reduction 315
– – by boranes, phosphoramide catalysts 317
– – by boranates, phase-transfer catalysis 318
– – by hydrosilanes, BINOLate catalysts 320

s
SALENs
– cyanide addition to aldehydes 136
Silyl enol ethers
– in aldol reaction 140, 154
– in Michael addition 50
Silyl ketene acetals
– in aldol reaction 142, 146
– in Mannich reaction 106
Stetter-reaction 227
Strecker-reaction 85
Substitution, nucleophilic 13

Sulfur ylides
– in the aziridination of imines 119
– in the epoxidation of aldehydes 211

t

TEMPO
– chiral TEMPO-derivatives for alcohol oxidation 306, 343
Thiazolium salts
– catalysts for the benzoin-condensation and the Stetter-reaction 228
Triazolium salts
– catalysts for the benzoin-condensation and the Stetter reaction 230
Thioethers
– catalysts for
– – aziridination of imines 119
– – epoxidation of aldehydes 211
– – Morita-Baylis-Hillman-reaction 188
Thiourea-based catalysts
– for the hydrophosphonylation of imines 126
– for the Mannich-reaction 107
– for Michael-additions 68
– for the Strecker-reaction 89, 401
Trichlorosilyl enol ethers 141, 154
Trifluoromethylation
– of aldehydes and ketones 205

u

Urea-based catalysts
– for the Strecker-reaction 89, 401

w

Wieland-Miescher ketone 170